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STUDIES ON RESISTANCE OF STAPHYLOCOCCI TO PENICILLIN: THE PRODUCTION OF PENICILLINASE AND ITS INHIBITION BY THE ACTION OF AUREOMYCIN

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The problem of bacterial resistance to the antibacterial action of antibiotics is not a new one. Of more immediate concern, however, is the observation that the percentage of micro-organisms, resistant on primary isolation to certain antibiotics, is definitely increasing. Thus Romansky (1) (1950) found that, in 1949, 58 per cent of the strains of Staph. aureus, 21 per cent of the strains of Staph. albus, 55 per cent of the strains of non-hemolytic streptococci, and 98 per cent of the strains of Strep. faecalis isolated from infectious processes were resistant, in varying degree, to the action of penicillin on primary isolation. Finland et al (2) (1950), in reporting on the *in vitro* susceptibility of pathogenic staphylococci to seven antibiotics, noted the changing (increased) resistance of staphylococci to penicillin in recent years.

The changing resistance of staphylococci to penicillin is even more strikingly brought out by the work of Barber (3, 4, 5). Studying the same population group in a hospital in 1946, 1947, and 1949, she found the percentage of resistant staphylococci to be 12.5 in 1946, 38 in 1947, and over 50 per cent in 1949.

Of the 115 strains of staphylococci studied by Bondi and Dietz (6), all of the 16 resistant strains produced penicillinase. None of the 99 strains susceptible to penicillin had this property. This observation was amplified by Spink and Ferris (7) (1947) who described two types of penicillin resistance for staphylococci. Resistance induced *in vitro* was temporary in character and was not associated with the production of penicillinase. Resistant strains isolated from patients who had been treated with penicillin, on the other hand, were permanently resistant and these strains produced penicillinase. Monnier (8) (1948) also emphasized the fact that the sensitivity of a penicillinase producing organism is a function of the size of the inoculum and the time of incubation.

The present study was undertaken in an effort to (a) determine the proportion of resistant staphylococci present in a variety of infectious processes, (b) compare this with the proportion of penicillin-resistant staphylococci isolated from the noses and throats of healthy carriers, and (c) test both resistant and susceptible strains for the production of penicillinase in an effort

to confirm the observation that there is a high degree of correlation between resistance and the production of penicillinase.

MATERIALS AND METHODS

The strains of staphylococci isolated from pathogenic processes were obtained in pure culture from the bacteriology laboratory of the Harriet Lane Home* and the general biological laboratory of the Johns Hopkins Hospital*. The source of each strain is given in Table I. The respiratory strains were isolated from nose and throat cultures of healthy individuals who sought employment in the Johns Hopkins Hospital* during the course of the study. Of the 50 pathogenic strains, 37 (74 per cent) were hemolytic Staph. aureus and 13 (26 per cent) were Staph. albus. Of the 25 respiratory strains 11 (44 per cent) were hemolytic Staph. aureus, and 14 (56 per cent) were Staph. albus. All strains of Staph. aureus from whatever source were coagulase positive while all strains of Staph. albus were coagulase negative.

The susceptibility of the strains to penicillin was determined by the serial two-fold dilution method standard (9) in this laboratory. The size of the inoculum routinely employed was a 10^{-4} dilution of the test strain. End points were recorded at the end of eighteen, forty-eight, and seventy-two hours incubation of the cultures and drug-dilutions.

The production of penicillinase was determined by the disc method. Plates containing 15 cc. of heart infusion agar were seeded with 1 cc. of a 10^{-3} dilution of a spore suspension of B. subtilis. The strain selected was known to be highly sensitive to penicillin and it did not produce penicillinase. After thorough wetting of the plates, the excess suspension was removed with a pipette and the plates were dried in the incubator for twenty minutes. Sterile filter paper discs, 12.7 mm. in diameter, were then saturated with broth containing (a) penicillin in three standard concentrations—2, 10, and 100 gamma per cc., and (b) penicillin to which had been added a sufficient amount of an eighteen-hour broth culture of the test organism to give a final concentration of 2, 10, and 100 gamma per cc. On the surface of each plate, prepared in the manner described above, two discs saturated with 2 test strains plus penicillin were applied together with one control disc saturated with penicillin alone in the same concentration. Thus it required three plates to test every 2 strains at concentrations of 2, 10, and 100 gamma per cc. The plates were incubated for eighteen hours, after which the amounts of penicillinase produced by the test strains were estimated by measuring the zones of inhibition surrounding the test discs as compared with the zone surrounding the control disc. By this method, a strain which produced a large amount of penicillinase would show no zones of inhibition in all three drug concentrations; a strain producing no penicillinase would exhibit zones of inhibition comparable to the controls in all three concentrations; a moderate penicillinase producer would show no zones of inhibition at concentrations of 2 and 10 gamma per cc., but a zone comparable with the control at 100 gamma per cc.

In an effort to find out if the production of penicillinase by a given strain could be augmented by repeated transfer in broth containing penicillin or decreased by repeated transfer in broth containing another antibiotic, the following experiments were carried out: Strain 8, a resistant strain, was tested for its susceptibility to aureomycin. It was then transferred daily in broth containing aureomycin in increasing concentrations for thirteen transfers and, as a control, the same strain was transferred daily in plain broth. Following this, the

* The authors are grateful to Miss Betty Fisher of the Harriet Lane Home bacteriology laboratory, Mrs. Isabelle Schaub of the Johns Hopkins Hospital biological laboratory, and to Miss Florence Williams of the Personnel Health Clinic of the Johns Hopkins Hospital for their assistance in collecting the strains for this study.

strain which had been transferred thirteen times in aureomycin was put back in penicillin broth and subcultured daily for thirteen transfers in penicillin broth. Strain 2, a sensitive strain, was transferred daily in broth containing penicillin for twenty-eight transfers, together with a control in plain broth. At the end of this period, these strains were re-tested for their susceptibility to penicillin and for their production of penicillinase. At the same time, 2 other sensitive strains of staphylococci, Cohen and MacLaughlin, which had been transferred for ten transfers in penicillin broth became available and they were tested for penicillin sensitivity and penicillinase production. From the same source (one of the authors) 1 penicillin-resistant strain of Aerobacter aerogenes and 1 penicillin-resistant strain of Klebsiella pneumoniae—both of which had been transferred for ten transfers in aureomycin, chloromycetin, terramycin, and streptomycin—were obtained. These strains were also tested for penicillin sensitivity and for penicillinase production.

RESULTS

By referring to Table I, it will be noted that 21, or 56 per cent, of the 37 strains of Staph. aureus and 5, or 38 per cent, of the 13 strains of Staph. albus were resistant to more than 1 gamma per cc. of penicillin. Of the combined total of 50 pathogenic strains studied, 26, or 52 per cent, were resistant to more than 1 gamma per cc. of penicillin. Of these, 3 (strains 23, 42, and 44) reached final end points of 1.56 gamma per cc. at seventy-two hours, while the other 23 were resistant to concentrations ranging from 3 to greater than 200 gamma per cc. Resistance was clearly demonstrable at eighteen hours in the case of 14 strains, and by the end of seventy-two hours in the other 12 strains. That this shift in the end point with prolonged incubation represents true resistance and not drug deterioration is shown by the fact that the 24 sensitive strains showed no such shift in end point no matter how long the incubation.

Direct confirmation of this observation is shown by the fact that, of the 23 highly resistant strains, only 1 (strain 21) failed to produce penicillinase; of the 3 strains of borderline resistance (1.56 gamma per cc.), 2 (strains 42, 44) produced no apparent penicillinase. These results, which are shown in Table I, bring out quite clearly the high degree of correlation between penicillin resistance and the production of penicillinase. That the converse is equally true is shown by the fact that, of the 24 strains sensitive to less than 1 gamma per cc. of penicillin, none produced penicillinase.

The results of the study of 25 respiratory strains of staphylococci are indicated in Table II. It can be seen that only 2, or 18 per cent, of the 11 strains of Staph. aureus and 2, or 14 per cent, of the 14 strains of Staph. albus were resistant to more than 1 gamma per cc. of penicillin and, unlike the pathogenic strains, 84 per cent of the respiratory, or 21 out of 25, were sensitive to less than 0.078 gamma per cc.. Only 4 strains, or 16 per cent, were resistant to concentrations ranging from 1.56 to greater than 25 gamma per cc.

None of the 21 sensitive strains produced penicillinase. All 4 resistant strains, however, produced penicillinase in varying degree.

TABLE I

Comparison of the In Vitro Sensitivity to Penicillin with the Production of Penicillinase by Pathogenic Strains of Staphylococci.

STRAIN NO.	SOURCE	STAPHYLOCOCCUS	COAGULASE	PENICILLIN SENSITIVITY (SERIAL 2-FOLD DILUTION)		PENICILLINASE PRODUCTION (ZONE OF INHIBITION (MM))		
				18 hr.	72 hr.	2γ	10γ	100γ
St. (1)	Umbilicus	albus	−	<0.78	<0.78	1.0	4.55	10.3
St. (2)	Ear	aureus	+	0.39	0.78	5.2	6.5	9.15
St. (3)	Bronchitis	aureus	+	12.5	>100.0	—	—	—
St. (4)	Surgical Inf.	aureus	+	3.12	12.5	—	—	—
St. (5)	Surgical Inf.	aureus	+	50.0	100.0	—	—	—
St. (6)	Surgical Inf.	aureus	+	3.12	3.12	—	—	7.57
St. (7)	Surgical Inf.	albus	−	0.78	0.78	3.75	8.0	10.25
St. (8)	Surgical Inf.	aureus	+	200.0	>200.0	—	—	—
St. (9)	Foot Inf.	aureus	+	12.5	>50.0	—	—	—
St. (10)	Surgical Inf.	aureus	+	0.039	0.078	3.0	7.65	10.0
St. (11)	Surgical Inf.	aureus	+	0.039	0.078	2.25	8.0	9.8
St. (12)	Surgical Inf.	aureus	+	0.019	0.039	5.0	7.5	10.5
St. (13)	Surgical Inf.	aureus	+	0.019	0.039	5.5	7.0	10.1
St. (14)	Pus (ear)	aureus	+	0.039	0.078	5.3	6.8	10.65
St. (15)	Furuncle	aureus	+	<0.045	0.09	5.5	7.75	10.3
St. (16)	Blood	aureus	+	<0.045	<0.045	3.73	8.62	11.49
St. (17)	Blood	aureus	+	0.039	>3.12	—	—	10.05
St. (18)	Surgical Inf.	aureus	+	<0.39	6.25	—	—	9.4
St. (19)	Surgical Inf.	aureus	+	0.78	>3.12	—	—	8.25
St. (20)	Surgical Inf.	aureus	+	<0.04	<0.04	5.5	7.65	10.0
St. (21)	Surgical Inf.	albus	−	50.0	50.0	2.05	6.5	10.5
St. (22)	Eye	albus	−	<0.04	0.09	5.65	8.05	10.4
St. (23)	Pus	aureus	+	<0.78	1.56	—	—	9.4
St. (24)	Pus	aureus	+	<0.78	12.5	—	—	8.0
St. (25)	Blood	albus	−	<0.78	3.12	—	7.05	8.8
St. (26)	Pus	aureus	+	<0.78	6.25	—	—	9.4
St. (27)	Umbilicus	aureus	+	12.5	>50.0	—	—	—
St. (28)	Breast Fluid	aureus	+	25.0	>50.0	—	—	—
St. (29)	Blood	albus	−	<0.78	<0.78	5.9	7.9	10.0
St. (30)	Skin Lesion	aureus	+	50.0	>50.0	—	—	—
St. (31)	Blood	albus	−	<0.78	<0.78	5.75	8.15	10.5
St. (32)	Pus	aureus	+	25.0	>50.0	—	—	—
St. (33)	Nose Culture	aureus	+	<0.78	6.25	—	—	9.5
St. (34)	Blood	albus	−	<0.78	<0.78	5.3	6.9	9.75
St. (35)	Spinal Fluid	albus	−	<0.78	<0.78	5.5	7.4	10.05
St. (36)	Ear	aureus	+	<0.78	<0.78	5.25	6.8	9.9
St. (37)	Thigh	aureus	+	<0.78	<0.78	2.15	5.4	9.05
St. (38)	Nose Culture	aureus	+	<0.78	<0.78	5.0	8.05	9.9
St. (39)	Blood	albus	−	<0.78	<0.78	4.9	8.0	9.5
St. (40)	Blood	aureus	+	>100.0	>100.0	—	—	8.15
St. (41)	Axilla	aureus	+	6.25	>50.0	—	—	7.55
St. (42)	Nose Culture	albus	−	<0.78	1.56	3.0	7.75	10.5
St. (43)	Nose Culture	aureus	+	<0.78	<0.78	7.0	9.0	10.5
St. (44)	Nose Culture	aureus	+	<0.78	1.56	4.15	5.0	10.55
St. (45)	Nose Culture	aureus	+	<0.78	<0.78	5.8	8.5	10.65
St. (46)	Nasal Washing	albus	−	<0.78	3.12	—	3.0	9.0
St. (47)	Eye	albus	−	1.56	6.25	—	—	8.65
St. (48)	Abscess	aureus	+	<0.78	<0.78	6.0	7.65	9.5
St. (49)	Nose Culture	aureus	+	<0.78	<0.78	6.5	8.3	11.0
St. (50)	Pus	aureus	+	<0.78	6.25	—	—	9.5
Controls (average)						3.08	5.5	10.+

Thirteen daily transfers of a resistant pathogenic strain, number 8, in broth containing aureomycin (in increasing concentrations from .05 to 1.56 gamma/cc.) resulted in a striking change in penicillin sensitivity and in the ability of the strain to produce penicillinase. As is shown in Table III, the strain which

TABLE II

Comparison of the In Vitro Sensitivity to Penicillin with the Production of Penicillinase by Respiratory Strains of Staphylococci.

STRAIN NAME	SOURCE	STAPHYLOCOCCUS	COAGULASE	PENICILLIN SENSITIVITY (SERIAL 2-FOLD DILUTION)		PENICILLINASE PRODUCTION (ZONE OF INHIBITION (MM))		
				18 hr.	72 hr.	2γ	10γ	100γ
Bi	Nose and Throat	aureus	+	<0.78	<0.78	7.5	9.1	10.5
Fo	Nose and Throat	aureus	+	<0.78	<0.78	6.15	8.25	10.4
Si	Nose and Throat	albus	−	<0.78	<0.78	6.0	9.25	10.5
He	Nose and Throat	aureus	+	<0.78	<0.78	6.5	9.5	11.7
Th	Nose and Throat	albus	−	<0.78	<0.78	6.9	9.5	10.9
Brau	Nose and Throat	albus	−	<0.78	<0.78	7.5	9.0	12.0
Bran	Nose and Throat	albus	−	<0.78	<0.78	7.0	8.55	9.9
Ha	Nose and Throat	aureus	+	<0.78	<0.78	7.5	12.0	14.6
Do	Nose and Throat	aureus	+	<0.78	<0.78	4.25	7.0	9.25
Wi	Nose and Throat	albus	−	<0.78	<0.78	7.5	12.0	15.5
Tr	Nose and Throat	albus	−	<0.78	<0.78	7.5	12.5	15.3
Bras	Nose and Throat	aureus	+	<0.78	<0.78	6.4	12.5	15.7
Cl	Nose and Throat	aureus	+	<0.78	<0.78	7.0	12.8	16.0
Bo	Nose and Throat	albus	−	<0.78	<0.78	6.5	8.5	10.8
Ja	Nose and Throat	aureus	+	<0.78	<0.78	6.15	7.3	10.5
Jo	Nose and Throat	aureus	+	<0.78	<0.78	6.8	10.5	10.8
Ed	Nose and Throat	albus	−	3.12	>25.0	—	10.0	11.15
Li	Nose and Throat	albus	−	<0.78	<0.78	6.55	10.5	10.0
Fa	Nose and Throat	albus	−	<0.78	<0.78	6.5	9.8	10.0
Bro	Nose and Throat	albus	−	<0.78	6.25	—	7.75	10.15
Ma	Nose and Throat	aureus	+	1.56	>25.0	—	8.5	10.4
Will	Nose and Throat	albus	−	<0.78	<0.78	7.15	8.0	10.8
St	Nose and Throat	aureus	+	<0.78	3.12	—	—	10.5
Ba	Nose and Throat	albus	−	<0.78	<0.78	6.0	7.65	11.3
Lo	Nose and Throat	albus	−	<0.78	<0.78	5.65	7.0	10.8
Controls (average)						3.08	5.5	10.+

originally had produced penicillinase and been resistant to 200 gamma of penicillin per cc. became sensitive to a concentration of 0.156 gamma per cc., and concomitantly ceased to produce penicillinase. This same shift in penicillin sensitivity from resistant to less resistant, accompanied by a decrease in ability to produce penicillinase, after exposure to aureomycin, chloromycetin, terramycin, and streptomycin† is also exhibited by the 2 gram-nega-

† In concentrations ranging from 2× up to 64× the original sensitivities of these strains to these antibiotics.

tive strains tested (Table III). On the other hand, repeated transfer of 3 sensitive strains of staphylococci (2, Cohen and MacLaughlin) in penicillin broth did not result in any capacity to produce penicillinase, even though resistance of the 3 strains was increased 100-fold, 4-fold, and 8-fold respectively. Likewise, repeated transfer of strain 8 in penicillin broth, following the thirteen

TABLE III

In Vitro Sensitivity and Penicillinase Production Before and After Exposure to Aureomycin, Penicillin and Other Antibiotics

STRAIN	PENICILLIN SENSITIVITY (SERIAL 2-FOLD DILUTION)	PENICILLINASE PRODUCTION (ZONE OF INHIBITION (MM))		
	18 hr.	2γ	10γ	100γ
Staph 8 (original)	200.0	—	—	—
Staph 8 (aureo)	0.156	7.0	8.5	12.5
Staph 8 (aureo, peni)	25.0	6.5	7.5	9.5
Aerobacter Aerogenes (original)	8000.0	—	4.5	12.0
Aerobacter Aerogenes (aureo)	250.0	6.0	8.5	11.0
Aerobacter Aerogenes (chloro)	250.0	5.0	8.0	12.0
Aerobacter Aerogenes (terra)	250.0	2.0	6.75	12.0
Aerobacter Aerogenes (strepto)	1000.0	7.5	9.0	12.0
Klebsiella pneumoniae (original)	>2000.0	—	—	12.0
Klebsiella pneumoniae (aureo)	500.0	7.0	8.5	12.5
Klebsiella pneumoniae (chloro)	125.0	7.5	8.5	12.0
Klebsiella pneumoniae (terra)	250.0	7.0	9.0	12.0
Klebsiella pneumoniae (strepto)	250.0	7.0	8.5	12.5
Staph Cohen (original)	0.06	7.0	10.0	13.5
Staph Cohen (peni)	0.24	7.5	9.0	13.0
Staph McLaughlin (original)	0.06	7.0	9.0	12.5
Staph McLaughlin (peni)	0.48	7.0	9.0	11.5
Staph 2 (original)	0.03	5.2	6.5	9.5
Staph 2 (peni)	3.12	7.5	9.0	12.5
Controls (average)		3.08	5.5	10.+

transfers in aureomycin, did not lead to the re-acquisition of the capacity to produce penicillinase in spite of the fact that the sensitivity of the strain shifted from 0.156 to 25 gamma of penicillin per cc.

DISCUSSION

In our study, which has been carried out during the fall of 1950 and the winter of 1951, over 50 per cent of the strains of staphylococci isolated from infectious processes were found to be resistant to penicillin. If this figure is compared with the 13.9 per cent figure reported by Bondi and Dietz in 1945, then the increase in the resistance of staphylococci over a five-year period is indeed striking. Since many, but not all, of our strains represent primary

isolations, we are not in a position to say how many of these strains acquired resistance during the course of treatment with penicillin. In these days of the widespread and indiscriminate use of penicillin, however, this question has become largely academic, because it would be an almost impossible task to prove that a patient had or had not taken or been given penicillin prior to admission to the hospital. But even assuming that some few strains, notably those isolated from closed systems such as the blood or breast, did acquire resistance during therapy, one is still left to speculate about the origin of some 20 odd resistant strains isolated from open infections. As Miller and Bohnhoff (10) have pointed out, there are three possible explanations: (a) that the strain has acquired resistance *in vivo* as the result of therapy; (b) that the site of the wound has become secondarily infected by a resistant contaminant of the same species; (c) that the bacterial population causing the infection consisted of a mixture of many sensitive and a few resistant organisms which were not detected in the original culture because they were overgrown by the greater number of penicillin-sensitive cells.

Our results would tend to emphasize the importance of the second possibility—that of cross-infection with resistant contaminants. This possibility seems likely for two reasons: (a) because of the high proportion of resistant strains (52 per cent) found in infectious processes as compared with the low proportion (16 per cent) found among the carrier strains; and (b) because the majority of the resistant pathogenic strains were isolated from open infections.

As was pointed out under *Results*, we found a high degree of correlation between penicillin resistance and the production of penicillinase. With only one exception, *all* the resistant strains isolated from pathogenic as well as non-pathogenic sources produced penicillinase in varying degree.

Another point deserves comment. Of the 26 resistant strains, 12 appeared to lie within the penicillin-sensitive range at eighteen hours incubation, only to shift into the penicillin-resistant range after seventy-two hours incubation. That this represented true penicillin resistance was borne out by the fact that all 12 of these strains produced penicillinase, in fact, the explanation for this shift would seem to be that penicillinase was being produced. That it can occur is of practical importance. It would explain, for example, the lack of response to penicillin therapy of certain infections caused by strains of staphylococci said to be sensitive to penicillin when tested in the usual manner. In the light of this observation, it would seem highly important to urge, when testing organisms for penicillin sensitivity, (a) that small inocula, comparable with those employed in testing the other antibiotics, be used routinely, and that (b) test dilutions be incubated for forty-eight hours and those showing a shift in end point be incubated another twenty-four hours in order to discover which strains are in the process of producing penicillinase.

Of perhaps greatest interest in this study is the observation that the capacity of a resistant strain to produce penicillinase can be inhibited or lost by exposure to another antibiotic, and that this loss is apparently irreversible. In the case of the resistant staphylococcus, strain 8, this loss of penicillinase producing capacity was accompanied by a shift in resistance from high degree to low degree, but re-acquisition of resistance did not lead to re-acquisition of the ability to produce penicillinase. Nor did repeated exposure of 3 non-penicillinase producing sensitive strains to penicillin result in any acquisition of capacity to produce penicillinase.

These observations would indicate that, although one of the manifestations of resistance of an organism is its ability to produce penicillinase, it is not the *sole* manifestation. If an organism which has once been a resistant penicillinase producer then becomes a sensitive non-penicillinase producer, and finally a relatively resistant non-penicillinase producer, obviously some mechanism is operating other than the production of penicillinase.

As to the mechanism whereby exposure to another antibiotic inhibits the production of penicillinase, two possibilities suggest themselves: (a) that the other antibiotic (aureomycin) blocks the enzyme system which is responsible for penicillinase production or (b) that the action of the other antibiotic is to eliminate the penicillinase producing organisms in any given culture by a process of selection.

The clinical implications of these observations deserve comment. If, during the course of an infection being treated with penicillin, the infecting organism is found to be a penicillinase producer, the substitution of another antibiotic to which the organism is sensitive is not only indicated but may at a later date allow the re-introduction of penicillin as a therapeutic tool, if the organism loses its capacity to produce penicillinase. In the case of staphylococcal infections, the substitution of aureomycin for penicillin would seem a logical procedure in the light of these observations.

SUMMARY

1. Of the 50 pathogenic strains of staphylococci studied, 56 per cent of the strains of Staph. aureus and 38 per cent of the strains of Staph. albus were resistant to more than 1 gamma per cc. of penicillin. Of the combined total, 52 per cent of the 50 strains were resistant to more than 1 gamma per cc. of penicillin.

2. Of the 25 respiratory strains studied, only 18 per cent of the strains of Staph. aureus and 14 per cent of the strains of Staph. albus were resistant to more than 1 gamma per cc. of penicillin. Of the combined total, 16 per cent of the 25 strains were resistant to more than 1 gamma per cc. of penicillin.

3. All but one of the resistant strains produced penicillinase.

4. None of the sensitive strains produced penicillinase.

5. Exposure to aureomycin brought about a loss in the capacity to produce penicillinase, and this loss appeared to be irreversible.

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THE THYROID HORMONE

Certain Aspects of its Elaboration in the Body, the Significance of its Structure, and of its Action on End Organs* †

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I have been asked to talk on the thyroid, even though to talk on the thyroid at Johns Hopkins where so much fundamental knowledge of the thyroid has been produced, is to bring carbonaceous material to North Britain. This is, however, an appropriate subject for me, because for thirty-five years, within the broader field of internal medicine, the diseases of the thyroid have been my particular interest, if you please, my scientific hobby. If I am qualified at all to give the Thayer Lectures, they must be on the thyroid. I am very grateful for this opportunity, and I shall make an all out effort to give you the essence of my experience and thinking on this subject. Be not dismayed, I shall not attempt any epitome of three and a half decades' worth of work in the Thyroid Clinic of the Massachusetts General Hospital. That would be intolerable. Rather I shall focus on certain selected items which I hope may indicate a point of view; an approach which makes use of the experiments which nature sets up for us in the clinic, and which amplifies such experience by suitably contrived experiments in the laboratory.

Because I believe that medical practice should rest on a firm foundation of scientific fact, I have sought, although a mere clinician, to penetrate as far as I am able, the biological and biochemical depths which underlie the clinical region with which I have been concerned. I do this with all humility and crave the indulgence of any pure scientists who may be present.

For my first lecture I have chosen to talk on the thyroid hormone—certain thoughts on what it is, how it is made, and what it does. In my second lecture I shall attempt to show how certain basic facts of thyroid physiology can be applied to problems of diagnosis and treatment.

In any consideration of the function of the thyroid gland, one is concerned largely with the thyroid hormone and with the thyrotropic hormone of the pituitary. The latter may conveniently be called thyrotropin. Our knowledge

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of these hormones is as yet fragmentary. We do know that together they form a balanced system, being reciprocally excitatory and inhibitory; the pituitary stimulating the thyroid and the thyroid inhibiting the pituitary, with respect to thyrotropic action. An example, to use present jargon, of the feed back principle.

The type of knowledge which we now possess of these two hormones is different. Thanks chiefly to the masterly work of Sir Charles R. Harington (1, 2), for example, we know a great deal of the biosynthesis of thyroxine. Of the mechanism by which thyroid hormone affects its targets, however, we know distressingly little. In the case of thyrotropin, the work of Rawson (3, 4), and of others, has given us some insight into the manner in which this hormone affects targets, but of its biosynthesis, or even of the rate of its production, we know nothing. The gaps in our knowledge are due, in part at least, to lack of certain technical approaches.

More work has actually been done by my own group in recent years on thyrotropin than on thyroid hormone, but as this has been rather fully discussed elsewhere, I have preferred in this lecture to concentrate on thyroid hormone. In the preparation of both lectures I have borrowed freely from the brains of many co-workers and associates, and I have drawn heavily from the pertinent literature.

I would like first to set a background for this discussion by recalling to you a few salient items of medical history. It is of interest that the first fundamental knowledge of the thyroid was gained largely by clinicians. Thus as early as 1820 Coindet in Switzerland showed that giving iodine relieved certain types of goiter, and in 1850 Curling in England found complete atrophy of the thyroid in sporadic cretins. The physiologist, Schiff of Geneva, in 1859 obtained hypothyroid manifestations in animals by thyroidectomy, but in 1874 Gull in England, although he gave an excellent clinical description of spontaneous myxedema in humans, stated that he was "not able to give any explanation of the cause." However, in 1883 the surgeon Kocher of Bern found that total thyroidectomy in humans produced the picture of Gull's disease. Finally substitution therapy for athyreosis emerged from the work of Bettencourt and Serrano, 1890, in France, and of Murray and of Fenwick in England, both of whom published in 1891. It was from such observations, as well as those of others, that the concept of a hormone peculiar to the thyroid gland took its origin (5).

This concept having been formed, the biochemists set to work to isolate an active principle. Baumann in Germany in 1896, discovered that iodine is a normal constituent of the thyroid, and by acid hydrolysis of the gland's proteins, he separated a small fraction containing about 10% of iodine, which

he called iodothyrin. This substance administered to patients with hypothyroidism was found to possess physiologic properties like those of whole thyroid gland.

The next event of first magnitude importance came two decades later (1915) when Kendall announced the isolation from the thyroid, in pure crystalline form, of the amino acid thyroxine, which he found to possess the full physiologic activity of whole thyroid, and to contain 60% by weight of iodine. Kendall stated then, and subsequent events have borne him out, that thyroxine is responsible for the entire physiologic activity of the thyroid gland. In 1911 another iodine bearing amino acid, diiodotyrosine, was isolated from the thyroid by Oswald, and very recently a third, namely, monoiodotyrosine, and it appears that these three amino acids between them, account for all the organically bound iodine present in the gland, and together they constitute from 90 to 95% of the total iodine of the thyroid. There is another 5 to 10% in inorganic form. Furthermore, it is of great interest that according to Harington, these tyrosine derivatives of the thyroid are the only iodine containing amino acids known to exist in nature (5).

The final crucial observations on the biochemistry of the thyroid hormone came in 1926 when Harington (6) identified the structural formula of thyroxine as an hydroxyphenylether of tyrosine containing four atoms of iodine in the 3:5 position, and the following year when Harington and Barger achieved its synthesis (7).

Harington and Barger synthesized thyroxine in the laboratory. It had never been done there before. But nature must have been biosynthesizing thyroxine in the bodies of animals for aeons, although we don't know just how far back in the evolutionary scale the process began. Harington and Barger's synthesis was accomplished by a complicated series of chemical reactions involving altogether, eight different steps, but their work disclosed that nature affects her biosynthesis by iodinating tyrosine to diiodotyrosine, and then by coupling two molecules of diiodotyrosine, with the loss of one side chain, to form one molecule of thyroxine.

The next bit of background that we need for what follows is that in the organism this synthesis seems to take place only within the matrix of a protein molecule. When the process occurs in the thyroid, the protein matrix is thyroglobulin. Whether there is any true *in vivo* extrathyroidal biosynthesis of thyroid hormone is a disputed question. If there is any it must be insignificant in amount. *In vitro*, however, a variety of proteins may be exposed to elemental iodine, and if pH be right, iodination of protein will occur, and thyroid-like physiologic activity will be acquired. This has been shown to be due to actual formation of thyroxine.

May I now add one final touch to the background? Then I will try to paint you a foreground. The point is that the thyroid gland does not operate in

glorious isolation. It is but a member of a coordinated system of endocrine organs functionally dependent on the nervous system, which two systems together, constitute the chief integrating mechanism of the higher animal organism.

The type of hormonal balance which I have already mentioned as existing between the pituitary and the thyroid, exists also between the pituitary and the gonad, and the adrenal cortex. Such "axes," as Salter (8) has called them, may exist in the case of other endocrines. They constitute self-regulating gadgets in which each of two glands involved is controlled through the blood level of the hormone of the other, and to some extent by that of its own.

When I began my career in medicine at the end of the first decade of the century, the tropic hormone of the pituitary had not been recognized as such. It was not until the late twenties that such terms as "thyroid stimulator" appeared, and the first use of "thyreotropic" that I am aware of is that of Crew and Wiesner in 1930 (9). Yet facts were available a century ago from which the existence of a pituitary thyrotropic principle could have been deduced. I refer to the fundamentally significant discovery of the French physician Nièpce (10), who in 1851, showed that the pituitary is characteristically enlarged in cretins. He had five autopsies; in each case the pituitary was hypertrophic. It is easy enough now to recognize the great importance of Nièpce's observation, but in the century which has elapsed since it was made, it has attracted but scanty attention. I would like to put in a plug for Nièpce.

I have called the pituitary-thyroid axis self-regulating, and so it is from the peripheral side. That is to say, it will presumably supply thyroid hormone to the body in relation to the use of that hormone by the body—the objective of the mechanism being the maintenance of a relatively constant level of thyroid hormone in the blood—an example, I should say, of what Cannon called homeostasis.

A similar situation has been shown, chiefly by the work of C. N. H. Long (11) and his collaborators, to exist in the case of the adrenal cortex. Control of cortical hormone output through blood level of the hormone acting on the AP, Long calls the "metabolic" control. However, he has further shown that there is another control mechanism which consists in the activation of the AP to put out ACTH, by adrenaline. This he calls the "autonomic" control. It may be considered a method of meeting emergencies. Whether there is an analogous "autonomic" control of thyroid function has not been established, but there are some reasons to believe that there is.

With this brief sketch of how the thyroid works in relation to the rest of the body, let us now turn to its intrinsic activities. These may be identified as being sequentially 1) trapping of iodide, 2) biosynthesis of hormone, 3) storage of hormone as thyroglobulin in the thyroid follicle, 4) discharge of

hormone to the circulation, 5) transport to targets, 6) action upon targets, 7) final fate of the hormone. I will examine certain aspects of some of these.

The thyroid gland is utterly unique in that for the manufacture of its hormone it requires an element—iodine—not used specifically by any other tissue. Without an adequate supply of iodine it cannot perform its function, namely, that of maintaining the metabolic rate of the body. It is not surprising, therefore, to find that it possesses a special mechanism for trapping iodide from the blood flowing through it.

When inorganic iodine is ingested and absorbed it circulates through the body as iodide. Like chloride, it is distributed chiefly in the extracellular fluid. When it reaches the thyroid it is specifically collected and concentrated. Thus the thyroid of the normal rat has been shown to concentrate ionic iodide as 20:1 as compared with the blood, and thyroids made hyperplastic with either thyrotropin or thiouracil can concentrate iodide up to 250 times the blood concentration. From the time that iodide reaches the blood stream from without, the thyroid and the kidney which excretes it, are in competition for it.

It is customary in thinking about thyroidal iodine, to distinguish between an inorganic fraction and an organically bound fraction. The former is freely dialyzable, the latter is non-dialyzable: the former can be discharged from the gland by an excess of thiocyanate ion; the latter cannot. Organically bound iodine in the thyroid is undoubtedly incorporated in the molecules of the three iodine bearing amino acids, which have been shown to be constantly present in the gland. It is in firm chemical combination. The achievement of this chemical union is an essential part of the process of hormone biosynthesis. It can be blocked by drugs of the thiouracil type. The amazing thing, however, is that the gland totally blocked in its synthetic activity by such a drug, still traps inorganic iodide as well as ever. The trapping mechanism can be divorced from the biosynthetic. The question is—what is its nature?

There are, of course, several levels at which the answer to such a question can be sought—those, for example, of naturally occurring disease, *in vivo* experiments on animals, and at the *in vitro* levels of intact living tissue (slices of thyroid), and finally of homogenates of one sort or another made from thyroid tissue. I will cite first some evidence gained from patients.

Stanbury and Hedge in our clinic were able to make radio iodine studies on three out of four goiterous cretins from a single family, and on one normal sibling; also on a single similar case from an unrelated family. These patients were sporadic, not endemic, cretins. Ordinarily sporadic cretins do not have goiters. In endemic cretins the goiter is a result of iodine want. When sporadic cretins have goiters some cause other than extrinsic iodine want must be looked for. Radio iodine tracer studies disclosed that the thyroid glands of the three cretins, and also of the normal sibling, all were able to accumulate iodide. On the administration of potassium thiocyanate the thyroids of the cretins

promptly discharged their iodide, whereas that of the normal sibling retained it. It was concluded that, whereas the cretinous members of the family were able to trap iodide in their thyroids in a normal manner, for some reason not known, perhaps an inherited imperfection in the iodinating enzyme system, they were unable to iodinate the tyrosine nucleus and so could make no hormone. Their goiters, which anatomically were no different from those found in severe endemic areas, were the expression of an intrinsic unavailability of iodine.

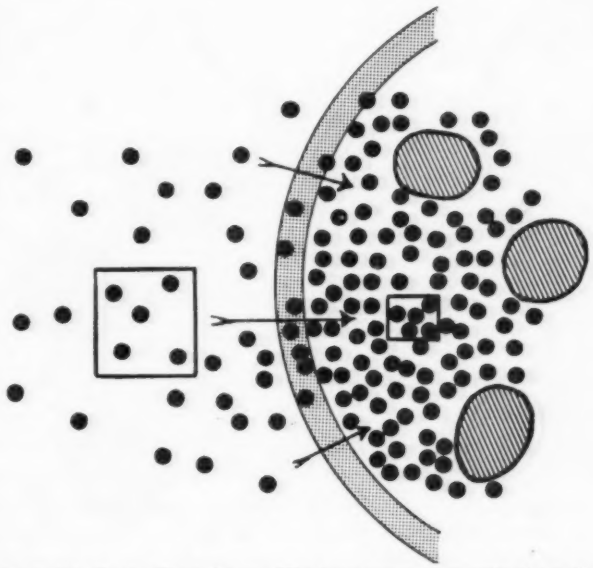


FIG. 1. *The Iodide Trap*—First theory. The long curve represents the wall of a thyroid cell. The black dots represent iodide ions and the three larger ovoid symbols represent protein molecules. According to this theory iodide is increted into the thyroid cell to reach a higher concentration than in the extracellular fluid.

The ease with which thiocyanate liberates or displaces iodide, or to put it another way, the high degree of reversibility of iodide collection *in vivo* suggests that its attachment in the thyroid must be very labile in nature. Two possible explanations of this process occur to one. First, as shown in Fig. 1 the thyroid cells may selectively increte iodide against a concentration gradient in a manner similar to the reabsorption process carried out by the cells of the renal tubules, or of the gastric mucosa with respect to the formation of hydrochloric acid, or of the concentration of potassium and magnesium by all cells. A second, and perhaps more likely explanation, is that iodide is simply adsorbed by some protein present in the thyroid cells which possesses

a specific affinity for the iodide ion, as shown in Fig. 2. If one could isolate the trapping mechanism and determine whether it requires energy, one might be able to choose between these two possibilities. The first would require energy, the second might not. However, I do not know how this could be accomplished.

The observations on the goiterous cretins led to studies now in progress at the *in vitro* level by Wyngaarden, Stanbury and Du Toit, in which use is made of certain acellular homogenates of thyroid tissue. Two types of material

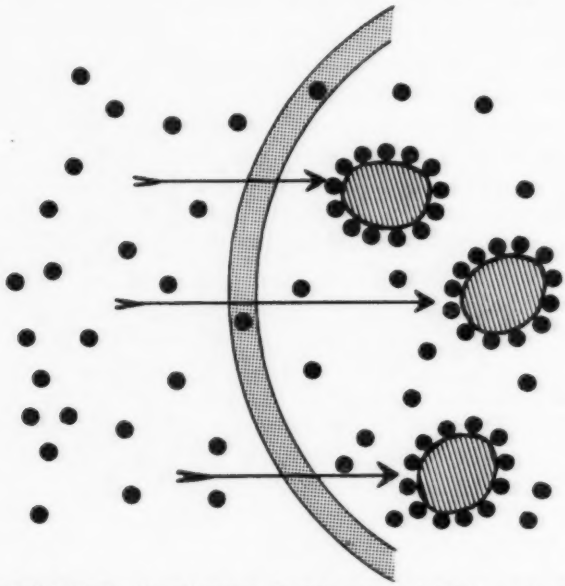


FIG. 2. *The Iodide Trap*—Second theory. In this case the iodide ions simply diffuse into the thyroid cell and become adsorbed on protein.

are being investigated, the thyroids of normal rats, and rat thyroids depleted of iodine. For control purposes other tissues than thyroid have been used—striated muscle, spleen, liver, kidney and blood serum.

Making use of I^{131} (radio actively labelled iodine) the trapping of iodide across a cellophane membrane by these materials, has been investigated. Dialysis is carried out for 72 hours at 1°C.

By this method it has been found that the homogenates of thyroid, whether normal or depleted of iodine, consistently bind iodide. The latter binds iodide in direct proportion to the concentration of iodide in the dialysate until a binding of one-tenth gamma of iodide per milligram of thyroid protein has been reached. The total binding of iodide by this homogenate exceeds its original concentration of iodide by two or more fold.

The other tissues studied bound only insignificant amounts of iodide, with the single exception of blood serum, which, when highly diluted, binds iodide two-thirds as well as thyroid. However, with serum on one side of the membrane, and thyroid homogenate on the other, the two being at nearly the same concentration of protein, the thyroid preparation will bind iodide from the serum.

By means of chromatography it has been possible to show that most of the iodide trapped in the thyroid homogenate is present in the form of inorganic iodide. Moreover, it has further been shown that the iodide which the homogenate binds is almost quantitatively precipitable with such agents as trichloracetic acid or zinc hydroxide, from all of which it is concluded that it is attached to, but not combined with, a protein molecule.

The next experiment was designed to discover whether the trapping of iodide by thyroid homogenates is reversible, as was that by the thyroid glands of Stanbury and Hedge's cretins. When exposed first to appropriate concentrations of thiocyanate, homogenates became unable to trap iodide. However, homogenates which had already trapped iodide did not release it when treated with thiocyanate, nor could it be dialyzed off from them. In other words, in the case of this *in vitro* iodide trapping, reversibility has not been demonstrated. The lack of reversibility of iodide trapping by the homogenate is puzzling. If the process is irreversible, iodide should not be present as such, and yet it is so present. Whether the trapping phenomena observed with homogenates are altogether different in nature from the iodide trapping exhibited by living cells, or are related to, or a part of the latter process, remains uncertain. The work is being continued in the hope of clarifying these points.

Another approach to the trapping problem has been through the study of the thiocyanate effect. Wyngaarden, Hedge and Stanbury have found that mole for mole iodide and thiocyanate, administered to the animal, are approximately equally effective in inhibiting the concentration of a labelling dose of radioactive iodine by the gland blocked with a thiouracil-like drug, or to put it another way, radio iodide occupying the iodide space of the gland can be discharged by equimolecular doses of either iodide or thiocyanate. On the other hand, it was found, using material labelled with S^{35} that the blocked gland is able to concentrate thiocyanate ion only to about ten times the serum concentration, whereas similar glands can achieve a concentration ratio for iodide 100 times that of serum, or better. The interesting paradox here is that, whereas the gland develops a much smaller concentration ratio for thiocyanate than for iodide, molar equivalent doses of the two have the same effect on the uptake of radioactive iodine given simultaneously. We have no adequate explanation for this paradox at present.

Following the trapping of iodide, the next step in the process which leads to the elaboration of thyroid hormone is the oxidizing of trapped iodide to iodine.

There is no free iodine to be found in the gland so that we must assume that on the oxidation of iodide, iodine is immediately combined with tyrosine to form first monoiodotyrosine and then diiodotyrosine. In contrast to the trapping of iodide, which may require no energy, the oxidation of iodide to iodine requires high energy. A peroxidase system is the only one known with high enough redox potential to promote this reaction, and Dempsey (12) and others have found peroxidase in the thyroid.

The next step, namely, the conversion of diiodotyrosine to thyroxine, requires less energy than the preceding, but nevertheless is believed also to be an enzymatically promoted reaction. It is accelerated by the action of thyrotropin.

The final event, that is to say, the delivery of thyroglobulin containing thyroxine into the follicles, Salter describes almost lyrically as follows: "The parenchymal cells spew their protoplasm out into the follicle much as lacteal (mammary) cells produce milk globules in the lactating breast."—perhaps a good analogy. "It is possible, therefore, that the manufacture of hormone can occur within the follicle proper, at least in part, by virtue of the naked protoplasm extruded from the parenchymal cells."

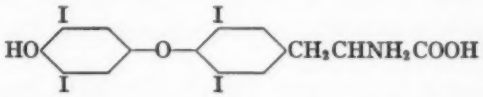
What determines the rate of release of hormone from the gland? This is important, for the rate of release determines the setting of the metabolic rate of the organism. It is well known that removal of the adenohypophysis is followed by atrophy of the thyroid and failure of hormone release. Conversely, administration of thyrotropin will maintain the structure and function of the thyroid in the hypophysectomized animal. It has not been clear, however, whether thyrotropin stimulates all phases of thyroid activity, or that this is seemingly so only because increased activity of one phase is followed *pare passu* by an increase in the next succeeding phase.

In an attempt to pinpoint the site of action of thyrotropin Goldsmith, Stanbury and Brownell measured the decay rate of radio iodine in thyroids of thyrotoxic subjects given an effective antithyroid drug, 1-methyl-2-mercaptoimidazole. When the decay curve, which is a straight line when plotted logarithmically, was well established, a series of injections of thyrotropin was given. Immediately there was a sharp increase in the decay rate. Since the factor of hormone synthesis was controlled by the blocking agent, the conclusion reached was that thyrotropin causes the release of hormone independently of its effects on trapping and synthesis. Whether there are other factors controlling the release rate remains for further investigation.

At this point it is appropriate to speculate about the significance of the structure of thyroxine. Although as previously said, there is reason to believe that this substance is synthesized within the thyroglobulin molecule, that it is stored in the follicles in chemical combination with thyroglobulin, that it is released from the thyroid by the enzymatic breakdown of thyroglobulin,

and transported in the blood stream in association with plasma proteins, nevertheless it seems now safe to assert that thyroxine itself either *is* the thyroid hormone, or at least the business part of it, the warhead, so to speak, of the torpedo! It is reasonable to liken it to a torpedo, for after all it is aimed at a target!

The thyroxine molecule we may well regard as a remarkable structure. Take a look at it.



It is the only known hormone which is an amino acid, and according to Harington, it is the only known naturally occurring product containing a diphenylether linkage.

Without an adequate supply of this potent compound normal life cannot go on, at least at the vertebrate level. It has no naturally occurring close relative that we know of—no great flock of related substances all having hormonic activity, as is the case with the steroids.

Let us scrutinize its architecture and see what inferences can be drawn as to why it is built the way it is. What are the functions of its several parts? To what does it owe its unique catalytic capacity? I well remember a lecture by Barger given in Boston in 1928, "It's as though," said he, "one tadpole had swallowed the tail of another.", and the eyes of the tadpoles are in positions corresponding to the Is of the molecule! We would like to know the function of its various components or radicals, as for example, the iodine atoms, the diphenyl arrangement, the coupling of the two benzene rings, the side chain (or tail, keeping the tadpole in mind) and the hydroxyl group at the "anterior" end.

A method of approaching this question is by the bioassay of analogues of thyroxine on suitable test objects, and the comparison of the result obtained as quantitatively as may be, with that obtained in the case of thyroxine itself. The effect on physiologic response of various departures in molecular structure can thus be identified. As a matter of fact, Harington and his co-workers started using this approach shortly after the synthesis of thyroxine, and during the intervening years a number of other investigators (13), including ourselves, have done likewise. The test objects have included normal and thyroidectomized animals in which the effect on metabolic rate is determined before and after the material is given, and tadpoles in which the effect on metamorphosis is quantitated. In our own work which started with Salter's return from Harington's laboratory in the autumn of 1929, with a bottle of thyroxine polypeptide in his pocket, and which has continued ever since, we have always made use of human beings suffering from spontaneous myxedema as our test objects.

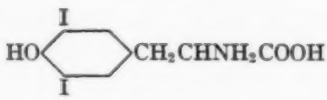
The objective has been to test every analogue of thyroxine that we could lay our hands on. Most of them were supplied to us by Harington. The work started off under the direct charge of Salter and Lerman, and after Salter's going to Yale in 1941, under that of Lerman.

It may be said at once that every variant from the thyroxine molecule, which has been assayed, has shown less physiological activity than the naturally occurring substance. In other words, any alteration that has been made in molecular structure has yielded a substance of diminished (or absent) physiological activity.

In the first place there is the matter of optical activity. Naturally occurring thyroxine is laevorotatory. When one gives parenterally pure dextrorotatory thyroxine, it produces a response about one-tenth that of pure laevorotatory in magnitude.

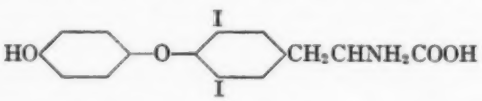
In our studies of thyroxine analogues conducted on patients with myxedema, we have always related the physiologic action (effect on basal metabolic rate) of the substance being tested, to that of pure laevorotatory thyroxine.

First we may consider the role of the diphenyl skeleton. For example, does diiodotyrosine



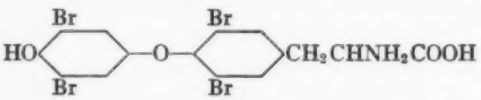
the building block from which thyroxine is made, have any physiologic activity? It is possible, but it is of a very low order of magnitude, about 0.005% that of l-thyroxine. All of the diphenyl compounds tested, provided they had any halogens, had far greater activity than diiodotyrosine. Thyronine with no halogens is inert, or nearly so.

A compound like thyroxine, but with only two iodines, 3-5 diiodothyronine



was 1.3% as active as thyroxine.

Substitution of bromine for iodine, namely, tetrabromothyronine

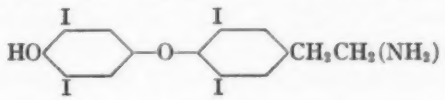


gave a compound 3.0%, and a tetrachloro variety 0.2% as active as thyroxine.

Thus it appears that the diphenyl structure is more important than having the right halogens, but also the right halogen is very important. Diiodothyro-

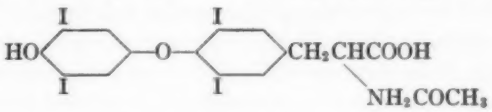
nine is less active than tetrabromothyronine, but more so than tetrachlorothyronine.

Thyroxamine, a substance with this formula tested by Gaddum (14)

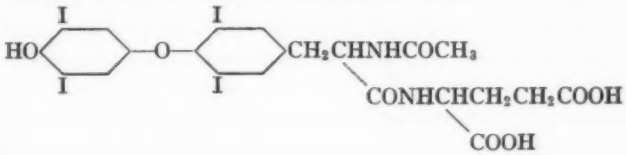


has little or no activity, which would indicate that the carboxyl group is indispensible.

Alterations in the side chain, however, other than removing the carboxyl, seem of relatively less importance. Thus N-acetyl 1-thyroxine

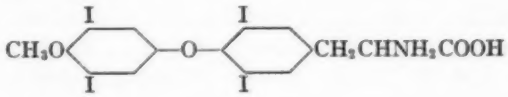


has 20%, and N-acetyl-d 1 thyroxyl-1-glutamic acid



has 5.5% the activity of 1-thyroxine.

Methyl ether of thyroxine



also has about the same.

Of still less importance is the coupling of the carbon rings by a sulphur, instead of the usual oxygen atom.

This gave a compound with 10.0% of the activity of 1-thyroxine.

Thus it appears that nature has discovered that in order for the thyroid gland to accomplish its function with the greatest efficiency, a diphenyl alanine is essential, and furthermore, that this must bear two or more atoms of a halogen, preferably iodine. The substitution of sulphur for oxygen in the coupling of the rings causes relatively slight deterioration in physiologic activity, and the same is true of certain alterations in the side chain.

Every component of the molecule seems to have its function, but just how this function is served remains obscure.

And now we come to the target. What influence does the hormone have upon the target, and how does it exert this influence?

We know in general terms that the target cell is speeded up in various ways. Its oxygen consumption is increased, and we also know that this increased consumption of oxygen is useful to the organism; that the energy released by the step oxidation of glucose is stored in high energy phosphate compounds, and becomes available to the cell and the organism as needed. It is not all degraded into heat, and blown off, to the detriment of the cells or the organism, as is the case when a substance like dinitrophenol is administered.

It is unknown in what form thyroxine gains entry to the cell, as a free dissolved substance, or in some sort of peptide combination. Does it enter by simple diffusion? Probably yes, because Lipmann has found it in approximately the same concentration in intra and extra cellular fluid. There is no accumulation of it, as there is of iodine in the thyroid cell. Does it alter the permeability of the cell membrane with respect to other substances? What does it do after gaining entry to the cell, and what happens to the hormone in the process? At least it can be said that the hormone appears to be metabolized in the body, presumably in the same fashion as any amino acid. Certainly too, it can be said that in some way it activates one or more of the enzyme systems of the cell. Lipmann has studied the distribution of thyroxine within the cell. Inasmuch as the mitochondria are known to be associated with the synthesis of adenosine triphosphate it was anticipated that a higher concentration of thyroxine might be found within them, but such was not the case. Lipmann found it in about equal concentration in the nuclear fraction of his homogenates, the mitochondrial fraction and the supernatant, which last represents the microsomes and soluble proteins of the cell.

One last point concerning the thyroid hormone which I should like to touch upon is the fundamental one of whether the output of hormone by the thyroid is determined by the call for hormone by the tissues, or whether the thyroid drives the tissues.

There are some bits of evidence which bear on this point. Rand, Riggs and Talbot (15) exposed rats to cold long enough to cause stimulation of the thyroid. Then they determined the protein bound iodine of the serum and compared it with that of rats which had been kept at room temperature. There was no difference. Dempsey and Atwood (16), have shown that when animals are exposed to cold more thyroid feeding is required to prevent thyroid enlargement than at room temperature. It appears, therefore, that under exposure to cold more thyroid hormone is put out, but does not pile up in the serum. From this it may be concluded that consumption of hormone is increased as

much as production, which favors the theory that tissue cells are calling for hormone. If the thyroid gland were driving the cells, one would expect the PBI of the serum to rise. All this is reminiscent of Barcroft's old concept of the call for oxygen by the tissues.

Harington in his Pedler Lecture (1944) (2) states that the terms of the lectureship require that "the lecture should indicate directions in which further work is required."

I do not know that any such condition has been imposed in the case of the Thayer Lectures, but for this particular one, at least, it is not inappropriate. I will, therefore, close this afternoon's discussion with certain suggestions as to how some of the gaps in our fragmentary knowledge of thyroid physiology might be narrowed. Actually I will mention five approaches, selected, be it understood without any thought of ultimate practical value or application.

First, it seems to me that much more study of the iodide trapping mechanism is indicated, and that this should be not alone from the point of view of the function of the thyroid gland, but with reference to, and for comparison with, other ion trapping mechanisms of the body. It seems likely that the principle involved in iodide trapping by the thyroid is not fundamentally unique to the cells of that organ, but has its analogues in the functions of other tissues. The inquiry has now got to the stage, however, in which the physical chemist must come to the aid of the biological or medical investigator.

Secondly, it is important to discover the mechanism whereby the pituitary-thyroid axis is controlled, as it must be, from the higher levels of the nervous system. What is the neuro-humoral pathway involved?

Thirdly the metabolic cycle of thyrotropin should be worked out. How is this hormone produced, and what determines the response of its end organs to it? We already know something of its excretion both in active and inactive form, but to get further on with the problem, we badly need a method for determining its titre in the blood stream, and in other tissues, as easy of performance as is the eosinopenic response as applied to the quantitation of adreno-corticotropic activity.

My fourth suggestion is that an all out effort be made to learn how thyroid hormone enters and affects its targets, and what happens to the hormone in the process. Is it consumed? Existing information indicates that it is, but how? It is not enough just to draw arrows from gland to target and let it go at that. Explorations in this area may well penetrate deeply into the fundamental nature of the act of living by the cell. It will require the services of enzymologists and physical chemists to solve this one.

Then also in the overall end organ problem is the fact that whereas thyroxine is a general somato-accelerator, when it comes to the cells, presumably the acidophyllic cells, of the anterior pituitary, it is an inhibitor, at least with

respect to thyrotropic function. It also seems to be a direct inhibitor of the cells that make it, the thyroid parenchyma. These facts too need study. Nothing is known of the mechanism involved at present.

Lastly, I would dearly like to see explorations of the largely unplowed field of the phylogeny both of the thyroid gland and of its hormone. I expect that it will be found that the hormone antedated the gland. To the practically minded this approach may appear nebulous, but I cannot but believe that it may prove to be productive of new biological concepts. Below the vertebrates no recognizable thyroid tissue has been described, but there is some evidence, not very satisfactory, that vertebrate thyroid may affect certain invertebrate species, even down to the level of the unicellular organisms. A search for all the iodine bearing amino acids from protozoon to vertebrate might shed light on the evolution of thyroxine. It seems to me nature can only have perfected this efficient hormone, this streamlined molecule, after many trials with simpler structures. It is thus, I believe, that the form of the living body and its component parts has come into being. Shall we not suppose that its biochemical anatomy has been similarly evolved? If it is worth while to trace the ancestry of an organ, why not that of a hormone also? The two combined will tell us the story of the organism.

And now I will have done! Tomorrow I will resume at a more clinical level.

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THE USE OF HORMONES, DRUGS AND RADIATIONS IN THE MANAGEMENT OF THYROID DISEASES*

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This afternoon let us shift our sights to a clinical level. Having now at our disposal a number of agents, the actions of which upon the thyroid gland, are known, or partly known, in precise biological or biochemical terms, let us examine the various ways in which they can be applied in the care of patients with diseases of the thyroid gland, or with disturbances of thyroid function. These ways will include diagnosis as well as treatment. Instead of the usual clinical approach, namely, of "how treat a given disease?," I wish to employ that of—"here is a tool; what is it good for?."

The tools I have grouped under the headings—hormones, drugs and radiations. I should perhaps have included surgical thyroidectomies, but that made the title too cumbersome. The diagnostic uses to which these tools can be put fall within the area of tests of function. The therapeutic uses fall within a certain framework which may be outlined as follows:

1. To suppress, or restrain, the pathologically over-active thyroid gland.
2. To augment the function of the pathologically under-active thyroid gland, or provide a substitute for it.
3. To alter the function of the normally acting thyroid in order to compensate for disturbed function elsewhere in the body (e.g., thyroidectomy or irradiation of the thyroid in certain cases of heart disease).
4. To remove or destroy mischievous thyroid tissue.
5. To obtain benefit through some extrathyroidal action of the agents in question (e.g., giving thyroid in the treatment of hyperophthalmopathic Graves' disease).

Let us keep this outline in mind as we proceed.

HORMONES

The hormones which I shall consider are thyroid hormone, thyrotropin, adrenocorticotropin and cortisone.

In the use of any of them I should like to distinguish sharply between physiological substitution therapy and pharmacotherapy. The former may be defined as the giving of a hormone, in cases of underactivity of an endocrine gland, in amount approximating what that gland would have made for itself under

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conditions of health. The pharmacotherapeutic use of hormones I should define as the giving of unphysiologically large doses of hormones, in order to obtain an alterative action which it is hoped may be beneficial to the patient. The administration of thyroid in myxedema is an example of the former; that of large doses of ACTH or cortisone, in rheumatoid arthritis, lupus, pemphigus, or what have you, is an example of the latter. Physiologic substitution therapy, simply because it is physiologic, is without danger of untoward side effects. Pharmacotherapy with hormones is beset with much danger. In these days of fantastic, and sometimes even reckless, empiricism in hormone therapy, it is desirable that we pause occasionally to get our bearings.

Thyroid Hormone. Since the first successful use of any hormone was with thyroid, we may appropriately begin our discussion with that. Back in the early nineties it was discovered that the feeding of thyroid is a full, perfect, and sufficient therapy for the relief of myxedema (primary athyreosis) or Gull's disease. Parenteral exhibition of pure thyroxine is equally effective, but possesses no advantage over the oral administration of whole thyroid. All this of course, is very ancient history, and I shall not belabor it further, except to stress one point, namely, that the relief of athyreosis by thyroid hormone is far more than merely raising the rate of energy metabolism. Dinitrophenol and related compounds, have a profound calorigenic action, but Dodds and Robertson (1) have shown that the BMR of a myxedematous subject can be raised from -20 to $+70$ by such a drug without there being any change whatever in the picture of athyreosis other than the rate of gas exchange. The action of thyroid hormone in physiologic dosage is utterly specific. No substances other than close chemical analogues of thyroxine can replace it, and the analogues must be given in far larger dosage than that of pure thyroxine to obtain a given effect.

There are uses, however, other than that of simple substitution therapy, to which thyroid hormone can be put, and of these I wish now to speak. Instead, for example, of using it for its general somato-stimulatory action, it can be used for its inhibitory action on such targets as the pituitary and the thyroid gland itself. When in Graves' disease the ophthalmopathy takes on a malignant type of course, it is customary nowadays to give thyroid to tolerance, the rationale being that the lesion results from excessive thyrotropic activity on the part of the pituitary, and that thyroid hormone inhibits the pituitary with respect to its thyrotropic function. This is all very fine provided the premises are correct. I am confident that there is adequate evidence that thyroid hormone inhibits the pituitary with respect to thyrotropic activity, but the relation of thyrotropin to malignant exophthalmos is, to say the least, uncertain. There is, of course, the production of exophthalmos in animals by thyrotropin, and there is a little evidence indicating a high titre of thyrotropin in the blood in malignant exophthalmos. There is also a very interesting recent

observation of Rawson's that labelled thyrotropin seeks the orbit (2), as well as the thyroid. But none of this evidence finally settles the problem. I have long suspected that changes in end-organ sensitivity, thyroid or orbital tissues, to thyrotropin, may play a role, but have no proof thereof. A great many patients with hyper-ophthalmopathic Graves' disease have been treated with thyroid, but so difficult is it to provide adequate control for clinical observations of this character, that I am at a loss to say whether or not any benefit is conferred by such therapy. At least I am convinced that I have never seen any harm result from it, and that's more than can be said of many forms of therapy. I even have seen improvement occur, but whether the result of the therapy, or a spontaneous happening, I cannot say with any certainty. A statement made to me by Purves of New Zealand when he visited us in 1949 is very pertinent in this connection. He is one of the few who have made determinations of blood thyrotropin level. He finds it elevated beyond normal in two conditions, myxedema and malignant exophthalmos. On the exhibition of thyroid in myxedema, blood thyrotropin level promptly falls to normal: in malignant exophthalmos, however, even very large doses of thyroid fail to alter it. This finding could be interpreted to indicate that there is no sense in using thyroid in exophthalmos as it appears not to exert the action desired of it. Certainly a better pituitary inhibitor is needed. A few observations have been made on ACTH in this connection, but the results are equivocal. Now we hear from France (3) of a remarkable new pituitary inhibitor, paraoxypropiophenone, a synthetic drug related chemically to diethyl stilbestrol. Nothing can be said about the effectiveness of this agent without more data, and because we desire a personal experience with it, we have obtained a small quantity and have started experiments with it.

Halsted years ago, here at Johns Hopkins, showed that removal of a large part of a dog's thyroid is followed by hyperplasia of the fragment left in situ. This we would now infer, must be due to increased thyrotropic activity of the pituitary. The giving of thyroid, or even of iodide, will prevent the development of hyperplasia of the thyroid remnant. Rienhoff (4), also in this hospital, has made use of this principle to prevent the regrowth of toxic goiters after subtotal thyroidectomy. More recently Cope in our clinic has made use of thyroid therapy in a related manner. Observing that in hyperfunctioning adenomata of the thyroid, the extranodular thyroid tissue tends to atrophy, he exhibited thyroid in cases of non-toxic goiter in order to bring any nodules which might be present into sharper relief by the expedient of causing atrophy of the extranodular thyroid tissue, so that the nature of the entire gland under study could be determined more accurately.

The use of thyroid in patients with habitually low basal metabolic rates, but lacking other evidence of hypothyroidism, needs mention. The etiology in such cases is really unknown, and the use of thyroid must be regarded as

pharmacodynamic and empiric. Often the metabolic rate in such cases is relatively unaffected by thyroid. Occasionally one hears stories of such patients taking up to a gram of thyroid per day without its having much observable effect upon them. One interesting fact has been unearthed by Farquharson (5) as a result of such therapy. He found that after the metabolic rate in these patients has been elevated by means of heavy dosage of thyroid, if the hormone therapy is then suddenly terminated, the basal metabolic rate falls to a lower level than that from which it started before thyroid therapy. We have called this the Farquharson effect, and believe it due to thyroid hypoplasia resulting from an excess of extrinsic thyroid hormone. The administered thyroid could cause such an effect either by pituitary inhibition or by direct inhibition of the thyroid, or by a combination of these.

We have run into this area in another way—a way which involves the diagnostic use of BMR, PBI and uptake of RAI. In spontaneous hyperthyroidism the values obtained by all these determinations are elevated. In true hypothyroidism they are all depressed. In thyrotoxicosis factitia, that is to say, due to ingestion of thyroid, BMR and PBI are elevated, but RAI uptake is decreased, this because the thyroid taken artificially causes hypoplasia, or at least hypoactivity of the subject's own thyroid. Such a formula is of high diagnostic significance, and useful in the detection of patients who surreptitiously take thyroid.

As a diagnostic tool the exhibition of thyroid is of limited importance. If one had been unable to arrive at a positive diagnosis in a myxedema-like picture, the presence or absence of characteristic response to thyroid would be of diagnostic significance. If while treating definite hypothyroidism with thyroid, the patient went into Addisonian crisis, the diagnosis of hypothyroidism due to primary hypopituitarism would be established.

Thyroid, like the glamour hormones of today, has been tried in many diseases. Good results from such trials have been few and far between. There is, however, one that is rather striking, namely, the relief of certain cases of sterility and of habitual abortion in women, by thyroid therapy.

So far as I am aware, the mechanism of the relief of sterility by thyroid is obscure. One is tempted to think that it may be a matter of acceleration of the energy transformation of the germ cells. On the relief of habitual abortion there is some evidence, Heinemann, Johnson and Man (6), for example, find that serum precipitable iodine rises during pregnancy, and that this rise antedates the customary rise in BMR. In women whose serum precipitable iodine did not make the expected rise, abortion was likely. When such women received thyroid during pregnancy their SPI curve followed a normal course.

Goldsmith, Sturgis, Stanbury, and Lerman (7) have made endometrial biopsies on women with untreated myxedema. It was found that such patients were bleeding from a proliferative, or oestrogen stimulated, endometrium. In

other words, they were not ovulating. The progesterone effect was lacking. One patient treated with APL, in the absence of thyroid therapy, ovulated. These facts suggest that thyroidless persons cannot produce LH the luteinizing hormone. In the case of two men with untreated myxedema of long standing, testicular biopsies showed striking absence of Leydig cells, which also is a finding suggestive of failure of LH production. In the absence of the thyroid hormone FSH can be made apparently, but not LH.

Thyrotropin. Although longer known than adrenocorticotropin, more is now known about the latter than the former. The reason for this is probably twofold. First, there is the widespread and intense interest in it which has resulted from the newly discovered and amazing pharmacodynamic action of cortisone, secretion of which hormone is promoted by ACTH. Second, there are easy quantitative tests for adrenocorticotropic action, such as the eosinopenic response, which are not available in the case of thyrotropic activity. Because of these circumstances it will be useful to bear the pituitary-cortical axis in mind as we consider the pituitary-thyroid.

When one wishes to bring about a remission in rheumatoid arthritis, he has a choice of two hormones, ACTH or cortisone. The effects of these on the patient as a whole are similar. In either case they are the result of increased supply of cortisone to the tissues. In one case the cortisone is given directly, in the other the patients' adrenal cortices are stimulated to put it out in increased quantity. It is a question of extrinsic supply of cortisone versus intrinsic. Although the effect on the patient's joint lesions may be identical in the two cases, that on his adrenal cortices is diametrically opposite. With ACTH his cortices are intensely stimulated; with cortisone they are put at rest.

Similar relationships occur between thyroid hormone and thyrotropin. I have discussed the use of thyroid, and now the question becomes—do we ever need to use thyrotropin therapeutically or in diagnosis?

In primary myxedema substitution therapy with thyroid is as near perfection as any therapy I know. There would be no point in using thyrotropin in this condition because the atrophic thyroid probably could not respond to it. In a case of pan-anterior hypopituitarism, however, one might expect to restore thyroid function by means of thyrotropin, and secure as good a total effect as with thyroid. But there is no reason to suppose it would be better. In panhypopituitarism there is also hypofunction of the peripheral targets of other tropic hormones. The patient fundamentally needs a new anterior lobe. In the absence of this one can provide substitution therapy either by giving peripheral hormones, thyroid, cortisone, estrogens, etc., or by giving tropic hormones, thyrotropin, adrenocorticotropin, gonadotropins, etc. Whether one course is better than the other in biological terms I do not believe we know today. However the pituitary hormones have the disadvantage that they may

provoke antibody production. Moreover, for more than experimental use, thyrotropin is at present unavailable.

The only diagnostic use of thyrotropin that I can at present visualize is in cases in which it is desirable to know whether or not the patient's thyroid gland is capable of being stimulated. Such use would constitute one method of distinguishing between primary thyroidal myxedema and myxedema of pituitary origin. There are other methods of accomplishing this purpose. Querido and Stanbury (8) have made observations of this character in our clinic. They employed BMR, PBI and RAI uptake as criteria of thyrotropic effect. In five out of six cases of primary myxedema there was no evidence of response to thyrotropin as judged by any of these criteria. In a sixth there was an increase in PBI and RAI uptake following thyrotropin, but none in BMR. In two cases judged to be of hypopituitarism on other grounds, there was marked increase in RAI uptake and in PBI after thyrotropin and in one a significant rise in BMR also.

The hypothesis has been raised that the so-called non-myxedematous hypometabolic rate cases represent a condition of end-organ insensitivity, that is, insensitivity of their thyroid glands to the action of thyrotropin. Querido and Stanbury had one such case in their series. This patient made a good response to thyrotropin, which would be evidence against end-organ insensitivity, but of course, much more is needed before any conclusion can be drawn.

Adrenocorticotropin (ACTH) and Cortisone. There is accumulating evidence that these hormones exert some depressant action on the activity of the pituitary-thyroid axis. Whether this is exerted at the pituitary level or at the thyroid level is not clear. Houssay and Stanbury (9) have observed six patients believed to have no thyroid disease, during periods when they were receiving ACTH for other diseases. Four of these showed striking depression of RAI uptake and PBI, but none of the six showed any change in BMR. The formula of decrease in RAI uptake and PBI, but no change in BMR, is an interesting one. A possible explanation would be that ACTH causes an increased sensitivity of somatic targets to the thyroid hormone. But there may be other explanations, although they do not occur to me at the moment. Four patients with rheumatoid arthritis treated with cortisone showed no change in either PBI or RAI uptake during treatment.

A number of investigators have used ACTH or cortisone in Graves' disease. The results are on the whole equivocal. Two patients treated with ACTH in our clinic showed no improvement in either the ophthalmopathy or thyrotoxicosis.

The use of cortical hormones in the toxic crises of Graves' disease (thyroid storm) antedates the introduction of cortisone. The nature of storm is still obscure, and as the condition is hardly ever met with in humans nowadays,

and cannot be produced in animals, the chance of solving the problem is not bright. We still hold to the hypothesis that storm represents what may be called decompensated thyrotoxicosis. It seems likely that the adrenal cortex is hyperactive in hyperthyroidism and somewhat better evidence exists that it is hypoactive in hypothyroidism. The thyroid and cortex seem to rise and fall together with respect to their functional activity. We have seen no literature on the eosinophile counts in storm, nor of autopsy material on the cortex either. Hyperthyroidism imposes a stress. The body responds to all stresses with adreno-cortical hyperfunction. It could be that in thyroid storm the cortex becomes exhausted and if this were true, it would be reasonable to administer cortical extract or cortisone.

DRUGS

The drugs I wish to consider are, on the one hand, iodine, and on the other, the growing group of so-called antithyroid or thyroinhibitor drugs. There are, of course, other drugs that are sometimes useful in the treatment of patients with diseases involving the thyroid gland—digitalis, quinidine, iron, vitamins, etc., but the use of them is really not germaine to the present discussion.

Iodine. It might be argued that iodine is not a drug at all, but a food, as are also iron and the other essential minerals. Certainly in the vertebrates from fish up, as shown by Marine, who started his career here, a minimal intake of iodine is essential to the preservation of health. The organism, whether fish or man, becomes goiterous when its iodine intake falls below a certain minimum, just as it becomes anemic with an inadequacy of iron, or asthenic during deprivation of salt, or osteo-malacic when starved of calcium. The prophylaxis of goiter in regions where environmental iodine is scarce, by feeding iodine, could be said to fall within the field of dietetics rather than of pharmacology. It is only in high mountainous areas or post-glacial regions of the earth that an external iodine shortage exists. In other parts there is invariably a superfluity of iodine so far as the needs of a normal organism are concerned, at least this is true unless there are present in the environment, simultaneously, positive goiter producing factors.

It was undoubtedly Chesney and his collaborators (1928) (10) here in this hospital who first clearly identified food factors as productive of goiter. Certain lots of cabbage were found to be the cause of an epidemic of goiter in his rabbit colony. Four years later Marine and his coworkers (11) showed that the food goitrogens were of the nature of cyanides, and all this recalled that back in 1905 Reid Hunt (12) had discovered the same phenomena in reverse, namely, that feeding thyroid protected animals against the toxic action of methyl-cyanide.

Twenty-three years elapsed between Hunt's discovery and Chesney's, and then it was another fourteen years before the great group of anti-thyroid drugs

were added to our therapeutic equipment. Man learns slowly, but fortunately occasionally he learns. He might have argued in 1905, if thyroid protects against cyanide, perhaps cyanide will protect against thyroid, but he didn't.

I will not pursue further at the present time the dietetic use of iodine. Let us rather seek to identify its uses in the treatment of established disease.

First, there is the matter of established endemic goiter. If this is etiologically a pure iodine-want affair, will giving iodine cause it to regress? As you well know, usually it will not. Why? I believe the reason is something like this. Under long continued iodine starvation, the thyroid, driven by the pituitary, becomes hyperplastic, and continues to make an abundance of thyroid protein, or thyroglobulin, even though it is unable to iodinate it. This iodine-poor colloid, being useless as hormone, is stored away in the follicles, which in consequence, get ever larger and larger. The familiar colloid goiter is produced. Structural changes, cystic degeneration, involution, etc., occur in the gland which ultimately become irreversible. Even when adequate iodine is finally supplied the swollen gland is incapable of shrinking to its normal size. What may happen under such circumstances if iodine is given, is that the iodine-poor colloid is rapidly iodinated, thyroxine is produced, and discharged to the body in excess. The patient becomes temporarily thyrotoxic. This is what Kocher long ago called "Iod-Basedow." It is rarely if ever seen in the United States, but only in the highly goiterous areas of the world.

The sporadic colloid goiters which one may encounter in non-endemic areas, and which differ anatomically from the endemic variety in no decernible way, are due, as in the case of Stanbury and Hedge's cretins, mentioned in yesterday's lecture, to some intrinsic functional defect—inability to iodinate tyrosine or to couple diiodotyrosine to form thyroxine, or perhaps in certain cases to collect iodine at all. Giving iodine to such persons will have no beneficial effect. It will not overcome the block to hormone synthesis. The administration of thyroid, only can be expected to accomplish any useful purpose.

However, in certain cases of goiter due to ingestion of a goitrogenic agent, either as food, e.g., cabbage, or in the form of medicine, the exhibition of iodine may be curative.

For a time there was a vogue of treating hypertensives with thiocyanate. It is, I am sure, on the way out, as is sympathectomy, and probably soon the rice diet. This is just a prediction, please pardon it. The point is that patients treated with thiocyanate sometimes grew goiters, and when they did, the goiters could be made to go away, and also the hypothyroidism which accompanied them, by merely administering iodide. Thiocyanate, as I stated yesterday, competes with iodide in the iodide trapping mechanism, and an excess of iodide will prevent the uptake of thiocyanate, just as an excess of thiocyanate will prevent the uptake of iodide. Of course a still simpler program would be to stop giving the patient thiocyanate. If, on the other hand, a goiter were due

to a drug of the thiouracil type, then giving iodide would be ineffectual because the primary difficulty under such circumstances would be in the iodination of tyrosine, not of collecting iodide.

The most important therapeutic use of iodine in thyroid disease, aside from that in the prevention or correction of iodine-want goiter, is in Graves' disease. The well known response to iodine of the thyrotoxicosis in that malady, remains, so far as cause and mechanism go, pretty much a mystery. This response and its mechanism has interested me for many years, ever since 1923 in fact, when Plummer brought it to the attention of the profession. In 1938 Lerman and I (13) analyzed the curve described by the BMR of patients with thyrotoxic Graves' disease during the administration of iodine. We compared it with the so-called thyroxine decay curve of Boothby and others, and found it to be altogether similar. From this we concluded that the action of iodine in Graves' disease is to stop, at least temporarily, the release of thyroid hormone from the thyroid gland. How this effect is exerted, or why it occurs in thyrotoxic patients, but not in normal persons, remains entirely obscure. In 1945 several of us made the observation that even when the thyroids of patients with Graves' disease are blocked with thiouracil, they still undergo involution when iodine is administered. In other words, it appeared that the iodinating action of iodine had been divorced from an involuting action. Again the explanation is not clear, but some later work of Rawson's, done while he was with us, may illuminate it somewhat. Rawson found in the first place that when thyrotropin acts upon the thyroid, it becomes physiologically inactivated. Later he showed that iodine interferes with the inactivation of thyrotropin by slices of thyroid, and that it inhibits the action of thyrotropin in hypophysectomized rats. Finally he found that patients with untreated Graves' disease excreted no active thyrotropin in their urine, but that after treatment with iodine they did excrete some. It was as though the untreated hyperactive gland was inactivating thyrotropin energetically, but that iodine interfered with this process and active thyrotropin spilled out in the urine.

Going back now to the nature of the iodine response in Graves' in the light of Rawson's last mentioned work, it may be that the divorce of iodinating and involuting action may be explained by the theory that iodine blocks the action of thyrotropin in thyroid cells, thus stopping thyroxine manufacture, but the thyroid cells go on manufacturing protein which piles up in the follicles and is not withdrawn therefrom, having no hormonic value. This theory does not explain why iodine does not have a similar action in normals, but concerning that another finding of Rawson's was that thyroids from thyrotoxic Graves' disease cases, inactivate more thyrotropin than normals. A change in end-organ sensitivity to thyrotropin may be at the bottom of the matter.

So specific to Graves' disease is the iodine response that in earlier days we

used it as a diagnostic test. Now with the newer diagnostic measures available, this seldom is necessary.

In treatment of thyrotoxicosis nowadays we seldom use iodine alone, but invariably use it in combination with an antithyroid drug, in the preparation of thyrotoxic patients for operation.

Antithyroid Drugs. As I have already indicated, these fall into at least two categories, that which blocks the iodine trapping mechanism, and those which block the synthetic process. The former is the thiocyanate ion, and the latter thiourea and its analogues, and some other substances with similar action.

Diagnostically these drugs may be used, as in the case of the cretins cited yesterday, to determine the location of a defect in the assembly line of hormone biosynthesis.

When it comes to therapeutics it may be said that, thus far, sulphocyanate does not appear to be of great importance. They might, to be sure, be used in controlling thyrotoxicosis, as suggested by Chapman, before the advent of the thioureas, but they are inferior to the latter for that purpose.

The thiourea analogues, of course, have made a great stir in the treatment of thyrotoxicosis, especially that of Graves' disease. They have also been used to produce hypothyroidism as treatment for certain forms of cardiac insufficiency. A huge amount of pharmacological work has been done on these drugs with a view to improvement in the molecule with respect to greater antithyroid action, and at the same time lessened tendency to produce toxic side effects. It has been, you might say, a process of pharmacologic streamlining. It is not my intention here to discuss the relative merits of the several drugs that have been tried. I am at present only concerned with the question—what have these drugs in general to offer in the treatment of thyroid diseases? In actual thyroid diseases, besides for thyrotoxicosis, they have only been tried so far as I know, in the treatment of thyroiditis, and it is my belief that for the latter purpose they really offer nothing. They also are used to produce hypothyroidism, when it is thought that hypothyroidism may be beneficial.

They are used widely as definitive therapy in Graves' disease, and to a lesser extent in toxic adenomatous goiter. For the latter they are certainly inferior to surgical thyroidectomy.

As definitive treatment in Graves' disease I personally do not like them as well as either radioactive iodine or surgical thyroidectomy. To get permanent remission of thyrotoxicosis in Graves' disease one must usually continue the administration of these drugs without interruption for at least a year, and even then one sometimes fails in one's objective. Surgical thyroidectomy removes thyroid tissue and radioactive iodine destroys it in situ, but the antithyroid drugs merely hold it in functional abeyance. To be sure if such control is exerted long enough, the disease may go into spontaneous remission during the period of treatment.

RADIATIONS

Radiations are used in cases of thyroid disease, both in diagnosis and in treatment. In treatment they are used, both x-ray and radioactive isotopes, for the purpose of destroying thyroid tissue either hyperplastic or neoplastic. Radium itself has been so used, but very infrequently, and hardly at all at present, so I will not say more about it. X-ray in treatment is hardly ever used nowadays in thyrotoxicosis, and in cancer it is only used in those cases in which all the malignant tissue cannot be removed and will not take up iodine.

In diagnosis x-ray is used to delineate goiters and demonstrate metastases. This use is familiar enough, and needs no further comment. Radioactive isotopes, chiefly of iodine, are used as tracers to see where they go, and the extent of their uptake. In addition to iodine, other isotopes may be used as tracers. Rawson has labelled thyrotropin with sulphur.

Radioactive Iodine. Radioactive iodine, chiefly I^{131}, has been extensively used in experimental work, notably by Hertz, Rawson, Chaikoff, LeBlond, Keating, Skanse, Dobyns, Stanbury, and others. I have touched upon some of this in Lecture I. I will not go further with it at present; instead let us consider the diagnostic situation.

Briefly the tracer situation can be said to resolve itself as follows: 1) the determination by direct scanning of uptake by the thyroid gland itself or distant thyroid tissue; 2) excretion—calculation of thyroid uptake by difference; 3) concentration and partition in the blood; 4) cytologic localization of iodine in the thyroid gland, or autoradiography.

The determination of total uptake of radio-iodine by the thyroid is useful diagnostically, chiefly in ruling hyper- or hypothyroidism in or out. It is highly instructive to compare it with simultaneous determinations of the level of protein bound iodine in the blood and basal metabolic rate. In spontaneous thyrotoxicosis all three values are elevated. In thyrotoxicosis factitia BMR and PBI are elevated. RAI uptake is depressed. The reasons for this were discussed in Lecture I. In phaeochromocytoma BMR may be elevated, but PBI and RAI uptake would not be. The explanation here is that the hypermetabolism is due to adrenalin, not to thyroxine.

In vivo, localized regional scanning is particularly valuable in determining the function activity of thyroid nodules as compared with the remaining extranodular and thyroid tissue. Some nodules can be shown to collect more radio activity than intranodular tissue, some less. In some cases there is little difference between them. We have dropped into the habit of calling those nodules which take up iodine briskly, "hot nodules;" those which do not, "cold nodules." There are to be sure a certain number of lukewarm nodules. Information of this character is diagnostically useful because there is a relatively high percentage of cancer in single nodules (18% of all single nodules in our

series). Single nodules are the easiest to scan directionally. Cancers take up less iodine than extranodular tissue. If a hot nodule is found, one can assume that the chance of its being malignant is negligible. On the other hand, the finding that a nodule is cold, raises an impressive possibility of malignancy. With such knowledge in advance the surgeon is better prepared to deal with malignancy if he finds it. He starts his operation ready to do a radical resection if indicated.

In older patients with heart disease the finding of a hot nodule suggests a hyperthyroid etiology, and raises the possibility of very marked relief by thyroidectomy.

Autoradiography locates function and correlates it with structure. We are getting new concepts of the significance of cytologic pictures. For example, certain hyperplastic adenomas are functionless while others with minimal hyperplasia may function actively. Many tumors which are forming colloid are not necessarily turning over iodine. Just because colloid is seen does not mean that the tumor can take up iodine. In this connection one is reminded of the divorce of iodinating action of iodine and its involuting action in Graves' disease which I mentioned earlier.

Treatment of Graves' disease by means of radioactive iodine has been under study in our clinic for ten years. In Hertz's original series there were 29 cases. Naturally in the beginning conservative dosage of radiation was employed with the result that in some of the cases control of thyrotoxicosis was incomplete and surgical thyroidectomy was performed later. Since 1943 Earle M. Chapman has had the assignment, and under his observations 315 patients with Graves' disease and 10 with toxic nodular goiter have been treated. Of these only four have subsequently required surgery. Fifteen have been over treated and required thyroid therapy. In three of them hypothyroidism was purposefully produced because of accompanying heart disease.

Of the four patients that were operated, the case of one was particularly instructive. This patient had Graves' disease, but with two incidental nodules. One of these was biopsied and found to be benign. Therefore the patient was treated with radioactive iodine, which relieved her thyrotoxicosis. However, the remaining nodule left in situ, persisted and caused some worry. It was accordingly removed and turned out to be carcinomatous. There was no way of knowing whether the irradiation had anything to do with its becoming malignant. It is believed that the surgical resection removed all the malignant tissue.

This case caused us to establish the policy of not treating nodular goiters with radioactive iodine.

Another worry was over the case of a patient from New Brunswick. She was treated with RAI for Graves' disease five years ago. Very recently we were informed that she had died of malignant disease believed primary in her thyroid and with multiple bone metastases. Some sections, both of thyroid

and bone lesions were sent to us, and our pathologists were quite certain that the case was one of multiple myeloma—not of thyrogenic cancer.

A third patient treated for Graves' disease with RAI died of widespread bronchogenic cancer with one small metastasis in the thyroid, but no patient in the whole series, so far as we know, has developed primary cancer of the thyroid. The late biopsies which have been performed show only fibrosis and regenerative hyperplasia.

Still we are worried about the possibility of producing cancer, and only until more years elapse and more patients are treated shall we feel that this ghost has been layed permanently.

The most encouraging therapeutic use of radioactive iodine is in the treatment of certain cancers of the thyroid. Of course in any type of thyroid cancer, as with any other cancer, the indication is to remove all malignant tissue surgically if that be possible. When this is not possible radioactive iodine can be used if the tumor will take up, or can be induced to take up, iodine. When no iodine uptake can be developed, then x-ray therapy is all that remains. Destruction of malignant thyroid tissue by radio iodine is to be preferred to x-ray, being more selective. The radioactive effect can be pin-pointed on the target to a far greater extent with radio iodine than with x-ray. The destruction of tumor, therefore, is maximal, and injury to other tissues minimal.

The plan of attack developed by Cope and Dobyns of our clinic is as follows: A tracer dose of RAI is always given preoperatively. If cancer is encountered, its iodine collecting capacity is determined by autoradiography of the excised tissue or by digestion of this and counting thereafter. If cancer tissue cannot be completely removed, then all normal thyroid tissue is removed. The Geiger counter can be used at the operation in the search for thyroid tissue. All tissue showing an uptake is removed. The reason for this tactic is to place the burden of thyroid hormone production entirely on the remaining cancer. Such a manoeuver may induce it to take up iodine. That is to say, a non-functioning cancer may be converted into a functioning one. If this can be accomplished radio iodine therapy may be employed with some hope of success. An example of this is shown in Fig. 1.

Our best results have been obtained in cases of the follicular type of adenocarcinoma, particularly distant metastatic lesions. In only a minority of papillary carcinomas can an iodine uptake be developed. Undifferentiated cancers seldom develop an iodine uptake, or at least kill the patient before an uptake can be developed.

Since the autumn of 1946 we have treated about 120 thyroid cancers with radioactive iodine. The most impressive effects are in the bone lesions. They remain, but stop growing, and they become asymptomatic.

I will mention three cases very briefly and then have done.

Mrs. M., with follicular adenocarcinoma of the thyroid, had a metastasis

to the humerus, with a pathologic fracture, and another in her ilium with limitation of motion in her leg. After RAI treatment the arm has healed, and she has regained perfectly good function of her leg.

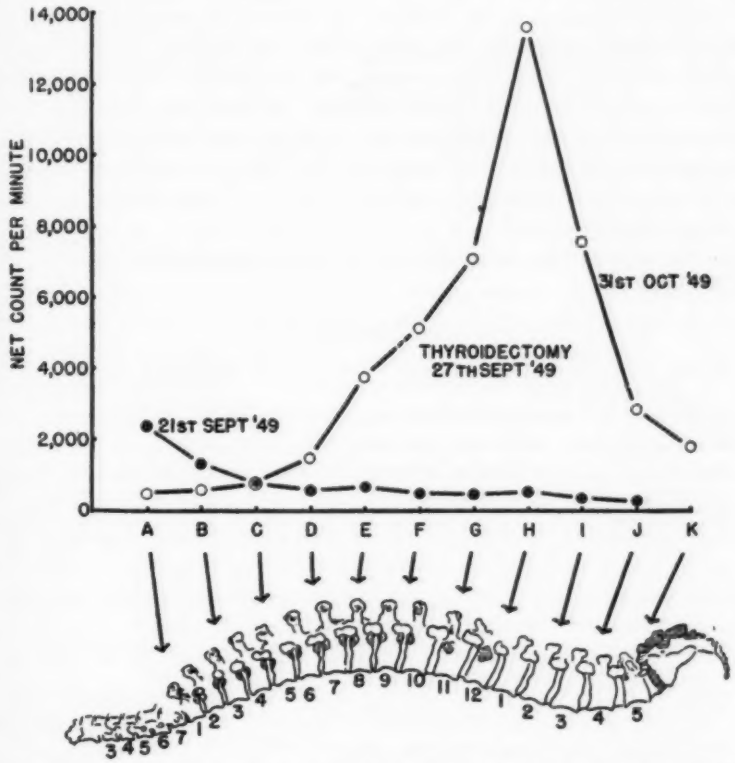

FIG. 1. *Effect of thyroidectomy on the avidity for iodine of a metastatic thyroid cancer in the lower dorsal spine.* (D11 & D12). Diagram indicates uptake of I^{131} over the several spinal segments before total thyroidectomy black dots, and 34 days afterward, circles. The ordinate shows the Geiger counter readings. It will be observed that a considerable iodine uptake was developed over the lesion, after thyroidectomy.

Mr. B. had a total thyroidectomy for cancer in 1946. He had metastatic disease in his spine with collapsed vertebrae and much pain. He is asymptomatic today with his cancer held in abeyance by RAI and his spine splinted by a successful bone graft.

Mrs. S.'s presenting symptomatology was pain in her right hip and buttock which caused a significant impediment to walking. By x-ray a destructive lesion of the bony pelvis was found and by biopsy it proved to be of thyroid

origin. A parent lesion was found in the thyroid gland. A total thyroidectomy was performed. Following this the metastasis developed an iodine uptake, and radioactive iodine therapy was used. As a result of this the bone lesion has been restrained and her symptoms have disappeared.

In conclusion I may say that what I have outlined are the chief measures we have today for controlling or modifying the activity of the thyroid gland within the body. Always it should be understood that such control is exercised exclusively for the good of the patient as a whole. Neither the thyroid nor any other organ is a therapeutic objective in itself. We may expect, as in any field, that if we engage in research, our methods of control will continuously be modified and improved.

For the opportunity to talk to you on these matters which fascinate me, I thank you.

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BLOOD VOLUME IN CONGENITAL CYANOTIC HEART DISEASE: SIMULTANEOUS MEASUREMENTS WITH EVANS BLUE AND RADIOACTIVE PHOSPHORUS

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It is well recognized that polycythemia is regularly seen in patients with congenital heart disease associated with right to left intracardiac shunts and cyanosis. However, there is not general agreement on the variation in the volumes of the fluid and cellular elements of the blood in these patients as compared with the variation of these elements in normal individuals. Polycythemia in cyanotic patients might conceivably reflect a diminished volume of plasma with a normal or an increased volume of cells, or a normal volume of plasma with an increased volume of cells, or even an increased volume of plasma with a proportionately greater increase in cell volume.

Previous studies of blood volume in patients with congenital cyanotic heart disease (1, 2) have entailed measurements of plasma volume by the Evans Blue dye method and calculation of whole blood volume from this value and the peripheral venous hematocrit. No data have been available heretofore concerning direct measurements of whole blood volume in cyanotic individuals.

Direct measurement of red cell volume or whole blood volume may be readily and precisely accomplished by preparing red cells tagged with radioactive iron or phosphorus, introducing them into the circulating blood of the subject and calculating the cell mass or blood volume from the eventual dilution of the tagged cells (3, 4, 5, 6). Incorporation of radioactive iron into the red cell is a relatively slow *in vivo* process. The iron method requires that a donor be available who is fed radioactive iron in relatively large quantities for an extended period of time in order to attain a concentration of radioiron in the donor's red cells adequate for quantitative determination after manifold dilution in the recipient's blood. The long half-life of radioactive iron and the requirement of a carefully prepared compatible donor make the method undesirable and cumbersome. On the other hand, radioactive phosphorus is incorporated rapidly *in vitro* into the red cells of a blood sample drawn from the ultimate recipient *himself* (6). The radioactive phosphorus remains in stable combination in the red cell and only about 6% is lost from the cells in an hour (7). These factors and the short half-life of P^{32} make it the preferable agent for use in the direct measurement of red cell or whole blood volume in clinical studies.

Combining the Evans Blue dye and radiophosphorus methods, we have

measured directly and simultaneously the plasma volume and the whole blood volume of 20 patients with congenital cyanotic heart disease who were admitted to the surgical service of the Johns Hopkins Hospital for study prior to operation. Each patient had polycythemia and cyanosis due to a right to left intracardiac shunt with diminished effective pulmonary blood flow. Similar studies have been carried out in 5 non-cyanotic convalescent adults.

METHOD AND PROCEDURE

The procedure followed is similar to that outlined by Evans and his associates (8). The tests were carried out in fasting subjects.

Twenty ml. of blood are drawn in a heparinized syringe from a brachial vein and transferred to a sterile heparinized 50 ml. centrifuge tube. With a tuberculin syringe approximately 50 microcuries of P^{32} as buffered isotonic radioactive phosphate solution (Abbott Laboratories, Chicago) are added. The tube is sealed with a rubber cap and gently agitated in a 37°C water bath for 2 hours by a mechanical shaker. The blood sample is then centrifuged at 3200 RPM for 10 minutes following which the plasma is quantitatively removed by a capillary suction tube. The red cells are resuspended in a volume of ice cold physiological saline approximately equivalent to that of the removed plasma, and after agitation and centrifugation for 10 minutes the saline is aspirated and discarded. This washing procedure is repeated once more and the cells are then prepared for injection by suspension in saline as before.

An accurate venipuncture is then performed upon the subject employing an 18 gauge needle and a blood sample (B_0) is withdrawn to furnish plasma for blanks during subsequent colorimetry and for determining a dye calibration curve. The needle is taped in place and connected to the small saline-filled infusion apparatus shown in Figure 1. This consists of a Luer-lok adapter and a 30 cc. asepto syringe barrel connected by a 12 inch length of plastic tubing (Tygon). A sufficient quantity of saline is allowed to run through the needle to be certain that the latter is securely in the vein. Into the infusion system is then introduced by quantitative pipettes exactly 10 ml. of the radioactive red cell suspension (C) and 1 to 3 ml. of 0.5% solution of Evans Blue dye (W. R. Warner & Co., Inc., New York). These substances are quantitatively rinsed into the vein by repeated additions of small quantities of saline (totaling approximately 40–50 ml.). The needle is withdrawn and the time of injection noted. The remainder of the radioactive cell-saline suspension is retained for determination of radioactivity.

After 15 minutes a final 20 ml. blood sample (B_1) is withdrawn from the arm opposite that used for injection. This specimen is placed in a heparinized receptacle. A five ml. aliquot of this final blood specimen (B_1) and of the remainder of the original tagged cell suspension (C) are placed in 6 cc. Sanford-Magath hematocrit tubes which are capped and centrifuged for 1 hour at 3200 RPM in a size 1-SB International centrifuge equipped with a No. 233 head whose radius is 20 cm. After the hematocrit of B_1 is read the dyed supernatant plasma is removed and designated P_1. The supernatant saline from the cell-saline suspension (C) is aspirated and discarded. To the residual red cells in each tube is added a sufficient volume of solution consisting of 1% saponin–0.1% sodium carbonate (with sufficient caprylic alcohol to prevent foaming) to bring the volume back to 5 ml. This accomplishes complete hemolysis of the red cells. The hemolyzed B_1 cells are diluted 5 times with 0.1% sodium carbonate solution. The hemolyzed C cells are diluted 833.3 times.[1] Triplicate 1 ml. aliquots

[1] 3 ml. diluted to 50 ml; 1 ml. of the resulting solution diluted to 50 ml. after addition of 10 ml. of hemolyzed blood prepared from B_0. This *in vitro* dilution is approximately equiva-

of diluted C and diluted B_1 are pipetted on to filter paper discs sealed by rubber cement into the bottom of small metal ointment boxes.[2] The hemolyzed blood is air-dried over night in

FIGURE 1. Apparatus used for simultaneous infusion of tagged cells and dye.

the ointment boxes at room temperature, and before counting drying is completed at 50°C for an hour.

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lent to the *in vivo* dilution of the injected suspension (C). Hemolyzed blood is routinely added in the dilution of C so that the weight of material present in 1 ml. aliquots of C would be approximately the same as that in 1 ml. aliquots of diluted B_1 in order to obviate possible counting errors due to differences in absorption. However, this is apparently an unnecessary step since the corrected average counts per second of duplicate boxes prepared from dilutions containing 0, 5 and 10 ml. of added hemolyzed blood were 7.93, 7.96 and 7.96 counts per second respectively.

[2] The presence of a filter paper (Whatman # 2) disc with a small amount of rubber cement apparently does not decrease the observed counts per second and promotes uniform spreading of the hemolyzed cells.

The radioactivity of all samples is determined with a lead shielded Geiger-Muller tube with a Mica window 2.2 mgm./cm.^{2} and a scaling unit. Background counts range from .36 to .48 counts per second. The surface area of the filter paper disc covering the bottom of the circular ointment box is 7.5 cm.^{2} and the box is placed in a well in a plastic tray so that it is always exactly 12 mm. distant from the window of the tube.[3] On each counting day the sensitivity of the tube is initially determined with a radioactive uranium oxide standard and during the day the background count is determined for a period of at least one hour. Routinely the time required for a minimum of 10,000 counts is determined in duplicate (rarely in triplicate) for each of 3 or 4 boxes prepared from dilutions of both specimens. Alternatively a continuous count of 20,000 is made on each box. Thus from 60,000 to 90,000 counts are made in order to calculate the average counts per second for each specimen. With one exception all specimens counted at a rate at least five times greater than background, while three-quarters of them counted at a rate more than ten times background. Counting is usually performed on the day after the experiment, but may be delayed for several days without affecting the ratio of counting rates.

Calculations with P^{32}

$$\underset{(WBV_{P32})}{\text{Whole Blood Volume}} = \frac{A_1}{A_2} \times V$$

Where:
A_1 is the measured activity in counts/sec./ml. of the injected cell-saline suspension (C)
V is the volume in ml. of the injected cell-saline suspension (C)
A_2 is the measured activity in counts/sec./ml. of the 15 minute blood sample (B_1)

$$\underset{(RCV_{P32})}{\text{Red Cell Volume}} = WBV_{P32} \times \frac{\text{Ht.}}{100}$$

Where:
Ht. is the hematocrit of sample B_1

$$\underset{(PV_{P32})}{\text{Plasma Volume}} = WBV_{P32} - RCV_{P32}$$

Plasma dye concentration is determined by diluting one or two milliliters of P_1 to a volume of six milliliters with physiological saline and reading the color intensity by the use of the Evelyn Photoelectric Colorimeter, employing an identically diluted solution of P_0 as a blank. Whenever the volume of P_1 permits, dilutions in duplicate or triplicate are read.

[3] Ten consecutive countings of the dried hemolysate in a single undisturbed box gave an average corrected count of 10.512 counts per second, a standard deviation of 0.132 counts per second, a coefficient of variation of 1.26 per cent and a standard error of the mean of 0.042 counts per second. Rotation of the box produces no significant alteration in the count. In one case duplicate aliquots carried through the entire procedure gave average corrected counts per second of 11.63 and 11.55 for C and 5.22 and 5.23 for B_1. In a second patient the average corrected counts per second for C were 11.49 and 11.34 and for B_1 7.33 and 7.48. In a third patient (normal control) the average corrected counts per second were 16.97 and 16.57 for C and 6.82 and 6.90 for B_1. Only in one instance do the two aliquots vary by more than one per cent from their mean value.

Both Filter 620 and Filter 540 M are used and any hemolysis present is corrected for by applying the following formula of Gibson and Evelyn (9).

$$\text{Corrected } L = \frac{20 \times L_{620} - L_{540M}}{20 - 0.6},$$

where L_{620} is (2—log of galvanometer reading employing Filter 620) and L_{540M} is (2—log of galvanometer reading employing Filter 540 M)

Calculations with Evans Blue

$$\underset{(PV_{T1824})}{\text{Plasma Volume}} = \frac{M \times K}{L_{620} \times d}$$

Where M is the milligrams of dye injected,
K is a calibration constant relating color intensity to dye content[4]
L_{620} is the average corrected L_{620} value, and
d is the number of times P_1 is diluted before reading.

$$\underset{(WBV_{T1824})}{\text{Whole Blood Volume}} = PV_{T1824} \times \frac{100}{100 - \text{Ht.}}$$

Where:
Ht. is the hematocrit of sample B_1.

$$\underset{(RCV_{T1824})}{\text{Red Cell Volume}} = WBV_{T1824} - PV_{T1824}$$

Preliminary studies employing Evans Blue dye in 10 patients with congenital cyanotic heart disease and P^{32} tagged red cells in addition in 4 of these indicated that a 15 minute interval was necessary for complete mixing of both dye and cells after injection into these polycythemic patients. On the average the concentrations of dye and P^{32} tagged cells were found to be 2.5 and 4 per cent greater respectively in the 10 minute specimen and 1.5 and 1 per cent smaller in the 30 minute specimen than those found in the 15 minute specimen. Because of the slow rate of dye disappearance after mixing it was deemed unnecessary to take multiple specimens for determination of a dye disappearance curve on subsequent patients in the study.

RESULTS

Table 1 shows a summary of the observations in the patients of this study. Group A consists of 2 male and 8 female cyanotic children ranging from 7 to

[4] For each patient the dye calibration constant, K, is calculated from readings made on solutions both stronger and weaker in color than that of diluted P_1. These solutions are prepared from a standard dye-plasma solution by adding known amounts of diluted plasma to aliquots of it. The standard solution consists of one volume of 10 mgm. % Evans Blue dye solution mixed with five volumes of diluted plasma. K is the average value determined by calculating k from the L_{620} value of each of three to eight suitable solutions by the following formula:

$$k = \frac{L_{620}}{c}$$

where c is the mgm. of dye per ml. of solution.

11 years of age, and Group B includes 5 male and 5 female cyanotic adults ranging from 16 to 27 years of age. For purposes of comparison data from 5

TABLE I

Summary of Observations in the Patients of this Study: Group A, Cyanotic Children; Group B, Cyanotic Adults; Group C, Non-cyanotic Adults

NO.	AGE (yr.)	SEX	WEIGHT (kg.)	HEIGHT (cm.)	SURFACE AREA (M^2)	PERIPHERAL HEMATOCRIT	PV_{T1824} (ml.)	RCV ($WBV_{Pm} - PV_{T1824}$) (ml.)	WBV_{Pm} (ml.)	'BODY' HEMATOCRIT
					Group A					
1	10	F	24.6	139.7	1.01	72.3	966	1274	2240	56.9
2	9	F	20.9	134.5	0.91	74.0	791	1192	1983	60.1
3	9	F	29.9	134.7	1.06	57.3	1073	787	1860	42.4
4	7	F	25.1	124.5	0.93	82.7	745	2365	3110	76.1
5	9	F	23.6	132.1	0.94	75.0	1158	1912	3070	62.3
6	7	M	15.7	101.6	0.65	71.7	535	788	1323	59.6
7	11	F	20.9	121.9	0.85	71.5	873	1224	2097	58.1
8	7	F	13.4	101.6	0.61	59.0	669	758	1427	53.1
9	8	M	24.1	114.3	0.86	78.0	844	1591	2435	65.4
10	11	F	27.3	142.2	1.06	76.5	943	1627	2570	63.3
Aver.			22.55	124.71	0.888	71.80	859.7	1351.8	2211.5	59.73
					Group B					
11	22	F	50.0	170.0	1.56	73.0	1615	2080	3695	56.4
12	18	F	51.6	157.3	1.50	74.0	1890	3280	5170	63.4
13	24	F	49.5	162.3	1.50	71.3	1693	2327	4020	57.9
14	18	F	48.6	160.0	1.48	72.5	1615	2160	3775	57.2
15	16	F	66.0	168.3	1.73	73.5	1897	2338	4235	55.2
16	20	M	46.4	166.2	1.48	86.5	1370	3820	5190	73.7
17	24	M	56.4	154.8	1.54	66.7	2148	2797	4945	56.5
18	27	M	53.6	172.7	1.62	84.3	2300	6500	8800	73.9
19	19	M	52.3	180.3	1.66	74.7	1893	2987	4880	61.3
20	21	M	54.1	175.3	1.66	76.3	2025	4175	6200	67.4
Aver.			52.85	166.72	1.573	75.28	1844.6	3246.4	5091.0	62.29
					Group C					
C1	36	M	66.0	175.2	1.79	35.0	2925	1165	4090	28.6
C2	28	M	63.2	167.5	1.70	52.0	2785	1215	4000	30.4
C3	22	M	69.6	187.5	1.93	42.0	3610	1580	5190	30.4
C4	66	M	51.2	165.2	1.55	49.5	2720	1350	4070	33.1
C5	40	M	84.0	174.0	1.97	44.3	3080	1745	4825	36.2
Aver.			66.80	173.88	1.788	44.56	3024.0	1411.0	4435.0	31.74

non-cyanotic convalescent adults are presented in Group C. In each instance plasma volume represents the value determined directly by the dye method

TABLE II

Comparison of the Averages of Directly Determined Volumes in Cyanotic Patients (Group A and B) with Similar Data in Non-cyanotic Patients, Expressed as Milliliters per Kilogram Body Weight

	NO. & SEX		AGE (YR.)	PERIPHERAL HEMATOCRIT	WEIGHT (Kg.)	PV_{T1824}	RCV_{Fe}	RCV ($WBV_{Fe} - PV_{T1824}$)	WBV_{Fe}	WBV ($PV_{T1824} + RCV_{Fe}$)	'BODY' HEMATOCRIT
Group A	2M & 8F	Average		71.80	22.55	38.71		60.15	98.86		59.73
		Minimum	7	57.3	13.4	29.7		26.3	62.2		42.4
		Maximum	11	82.7	29.9	49.9		94.5	130.0		76.1
Group B	5M & 5F	Average		75.28	52.85	34.92		61.93	96.85		62.29
		Minimum	16	66.7	46.4	28.7		35.4	64.1		55.2
		Maximum	27	86.7	66.0	42.8		121.3	164.1		73.9
Group C	5M	Average		44.56	66.80	45.98		21.34	67.32		31.74
		Minimum	22	35.0	51.2	36.6		17.6	57.4		28.6
		Maximum	66	52.0	84.0	53.1		26.4	79.5		36.2
Nachman, James Moore & Evans (8)	36M & 2F	Average		44.95	63.18	45.28	29.47			74.74	39.40
		Minimum	17	27.6	42.0	26.3	14.6			45.8	21.7
		Maximum	87	61.5	91.5	60.5	43.5			95.7	48.8
Reeve & Veall (7)	13	Average		44.71	71.63	47.05	30.15			77.20	39.06
		Minimum		40.1	60.5	39.8	26.0			68.2	35.5
		Maximum		49.6	94.1	52.2	33.7			83.4	42.8
Noble & Gregersen (10)	51M	Average				44.7					
		Minimum				34					
		Maximum				58					
Kelly, Simonsen & Elman (11)	9	Average							69.81		
		Standard deviation							7.79		

and whole blood volume is the value obtained by direct measurement with the radioactive phosphorus procedure. Red cell volume is presented as the difference between these two directly determined values. This quantity in turn is divided by the directly determined whole blood volume to obtain the "body" hematocrit of each patient.

TABLE III

Comparison of Observed and Predicted Values for Plasma Volume in 10 Cyanotic Children

PATIENT NO.	1	2	3	4	5	6	7	8	9	10
Observed PV_{T1824}	966	791	1073	745	1158	535	873	669	844	943
Predicted PV_{T1824} (12)	1375	1250	1250	1050	1200	633	1000	633	850	1425

TABLE IV

Comparison of Averages of Directly Determined Volumes of the Patients of this Study with Averages of the Volumes Calculated by Use of Peripheral Hematocrit

TRAPPED PLASMA CORRECTION	HEMATOCRIT		PLASMA VOLUME		RED CELL VOLUME			WHOLE BLOOD VOLUME		$\frac{RCV_{Pm}}{RCV_{T1824}}$
	Peripheral	'Body'	T1824	Pm	T1824	Pm	($WBV_{Pm} - PV_{T1824}$)	T1824	Pm	
					Group A					
None	71.80	59.73	859.7	592.7	2382.2	1618.4	1352.0	3241.9	2211.5	0.696
4%	68.91			662.7	2033.0	1548.8		2892.7		0.772
8.5%	65.70			730.2	1735.4	1481.3		2595.1		0.861
					Group B					
None	75.28	62.29	1844.6	1208.9	6102.0	3882.1	3246.4	7946.6	5091.0	0.650
4%	72.24			1365.2	5089.4	3725.8		6934.0		0.735
8.5%	68.87			1538.1	4253.9	3552.9		6098.5		0.829
					Group C					
None	44.56	31.74	3024.0	2466.0	2468.0	1969.0	1411.0	5492.0	4435.0	0.812
4%	42.76			2544.4	2287.0	1890.6		5311.0		0.840
8.5%	40.76			2632.6	2100.0	1802.4		5124.0		0.872

Although the red cell volume in 19 of the 20 cyanotic patients is greater than the respective plasma volume, the increase is less than would be anticipated from the levels of the peripheral venous hematocrit. The "body" hematocrit in each instance is appreciably smaller than the peripheral value. However, the average "body" hematocrit of the 20 cyanotic patients is almost twice as large as that of the non-cyanotic group. It is interesting that the one cyanotic patient with red cell volume smaller than plasma volume has the lowest peripheral hematocrit of any of the cyanotic patients.

Table 2 presents a comparison of the averages of the directly determined volumes on a weight basis of the patients of this study with similar data obtained by other investigators (7, 8, 10, 11) from non-cyanotic patients. It is seen that the cyanotic patients in both groups A and B have a diminished plasma volume, a greatly increased red cell volume, and an elevated whole blood volume when compared with the average values of the non-cyanotic patients. There is a remarkable parallelism in the volumes of the cyanotic children (Group A) and those of the cyanotic adults (Group B) when the values are expressed as milliliters per kilogram of body weight.

It is probably inappropriate to compare the blood volume data of the cyanotic children with "normal" standards of non-cyanotic adults. In Table 3 the observed values for PV_{T1824} in the 10 cyanotic children are compared with the values for PV_{T1824} predicted for these children from the nomogram of Brines, Gibson and Kunkel (12) employing height as a standard of reference. It is seen that 7 of the children have a diminished plasma volume while 3 others have essentially normal values. No data are available concerning direct measurements of red cell volume or whole blood volume by the radiophosphorus method in non-cyanotic children.

Table 4 presents a comparison of the averages of the directly determined plasma, red cell and whole blood volumes of the patients of this study with the averages of the volumes calculated by the use of the peripheral venous hematocrit. The latter include values for red cell volume and whole blood volume calculated from PV_{T1824} and estimates of plasma volume and red cell volume calculated from WBV_{P32}. The discrepancies between direct and indirect estimates of the various volumes are apparent in the table. These discrepancies are diminished by correction of the peripheral hematocrit for "trapped" plasma. The table includes averages of calculated volumes based on the peripheral hematocrit uncorrected for "trapped" plasma, corrected for 4% "trapped" plasma (13), and finally corrected for 8.5% "trapped" plasma (14). It is evident that the larger the correction which is applied to the hematocrit, the more nearly do the ratios (RCV_{P32}/RCV_{T1824}) approach unity.

DISCUSSION

The results of this investigation indicate that in patients with congenital cyanotic heart disease of the types associated with right to left intracardiac shunts and reduced effective pulmonary blood flow there is a diminished plasma volume, a greatly increased red cell volume, and an elevated whole blood volume (Figure 2). These findings are in general agreement with those observed in isolated cases by Meyer (15) and Blumenfeldt and Wollheim (16), and in the two cases studied by Hallock (1). Using the Evans Blue dye method alone, Nelson, Mayerson, Clark and Lyons (2) studied 7 patients with tetralogy of Fallot and found similarly elevated red cell and whole blood volumes, but

normal or slightly elevated values for plasma volume. Simultaneous measurements with Evans Blue and radiophosphorus in the 20 cyanotic patients of the present study show that plasma volume is usually reduced below normal levels by both direct and indirect methods of measurement.

Berlin, Lawrence and Gartland (17) found low plasma volumes and elevated red cell volumes in two patients with tetralogy of Fallot employing the radiophosphorus method alone. These investigators also found similar changes in

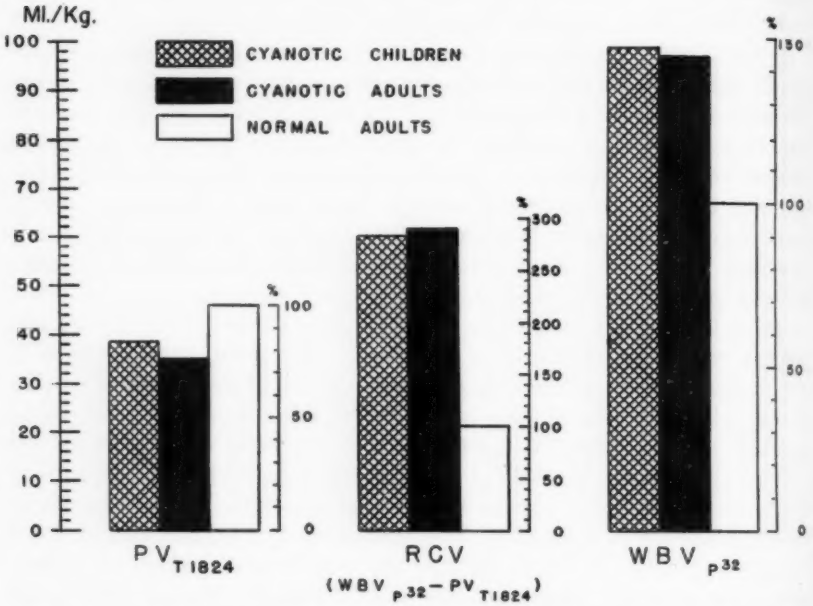

FIGURE 2. Graphic comparison of the average directly determined volumes in the 3 groups of patients studied.

plasma and red cell volumes in the majority of patients with polycythemia vera which had peripheral hematocrits of 55 or greater.

It is interesting that there are no striking differences in the present study between the volumes of the cyanotic children and those of the cyanotic adults when the values are expressed as milliliters per kilogram of body weight. No data are available concerning blood volume in infants with congenital cyanotic heart disease. It is well known, however, that the peripheral hematocrit usually rises progressively in the first few years of life in such patients (18). The present study suggests that maximal polycythemia and hypervolemia may be attained in mid-childhood and that no significant alteration in the polycythemic pattern occurs after this period.

The various sources of error in the dye-dilution and tagged red cell-dilution techniques for measuring circulating blood volume have been ably discussed recently in articles by Elman (11), Evans (8), Price (19) and their respective associates. Although an apparently adequate mixing time has been used in the present study, factors peculiar to the circulation of polycythemic patients with congenital cyanotic heart disease may reduce the accuracy of the sampling, particularly when peripheral venous blood is used. The error introduced by the peripheral hematocrit in indirect estimates of plasma, red cell or whole blood volume is magnified in polycythemic subjects (Table 4). Berlin and his associates (17) have shown that the variation of the red cell volume for a given hematocrit is so great that it is not possible to predict total red cell volume from the peripheral hematocrit in polycythemic patients. The present study minimizes this source of error as it is based on direct measurement of plasma volume by dye and of whole blood volume by P^{32} tagged cells.

It is well known that the polycythemia of patients with congenital pulmonary stenosis and right to left intracardiac shunts is reduced by appropriate surgical procedures such as the creation of an artificial ductus arteriosus (20). It should be of interest to study by direct measurement the changes in plasma, red cell, and whole blood volume which take place in these patients after operation. Studies of this type are in progress.

SUMMARY

Combining the Evans Blue dye and radioactive phosphorus methods simultaneous direct measurements of plasma volume and whole blood volume have been carried out in 20 patients with congenital cyanotic heart disease and in 5 non-cyanotic convalescent adults. The results are presented in tabular form and are compared with similar data obtained by other investigators from non-cyanotic subjects. Cyanotic patients in both childhood and adult groups have diminished plasma volume, greatly increased red cell volume and elevated whole blood volume when compared with non-cyanotic individuals. There are no striking differences between the volumes of the cyanotic children and those of the cyanotic adults when the values are expressed as milliliters per kilogram of body weight.

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INADVERTENT GASTRO-ILEOSTOMY: SUCCESSFUL OPERATIVE CORRECTION SIX YEARS AFTER GASTRECTOMY

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Digestive symptoms of either mild or transitory nature not infrequently follow operation in patients subjected to subtotal gastric resection (1). Fortunately, in few of these patients will such symptoms prolong convalescence or detract from the overall success of the operation.

Persistent or disabling symptoms following gastrectomy should arouse suspicion of technical errors committed at the time of operation. This report deals with a case of long survival after gastric resection and inadvertent gastro-ileostomy. This mistake appears to be uncommon. Moretz (2) in a recent review could find only two reported cases of gastric resection complicated by inadvertent gastro-ileostomy and added a third. He suggested that as with most surgical mishaps, the condition might not be as rare as indicated by the paucity of reports.

CASE REPORT

Mrs. C. W. (#256061), a 52 year old white farmer's wife, was admitted to the medical clinic of The Johns Hopkins Hospital on December 7, 1949 with severe malnutrition and multiple fractures. Six years before she had undergone subtotal gastric resection at another hospital for a peptic ulcer. Since that time she had never felt well and had suffered progressively failing health and emaciation. She had been completely bedridden since early 1949.

In the immediate postoperative period tube feedings and pureed foods were given without untoward effects. However, when solid foods were added two weeks after the resection, certain constituents appeared intact in the stools one to four hours after ingestion. Nevertheless, the patient was discharged on a regimen of bland diet and antispasmodics. Two months after the operation she passed tarry stools, and simultaneously hemorrhagic areas appeared in the skin of the lower arms. These skin lesions persisted and bled with the slightest trauma. In the meantime her weight fell from 140 pounds before operation to 100 pounds.

Five months later the patient was re-admitted to the same hospital. A barium enema disclosed no evidence of gastrocolic fistula. An upper gastro-intestinal study was considered to be normal except that barium was noted in the caecum in 20 minutes, this finding being attributed to "hypermotility."

During the first year after operation the stools gradually became bulky, pale, and of mushy consistency. The number of stools varied from eight to twelve daily. Recently the patient had learned to avoid fatty foods and thus to limit the number of stools to three or four per day. There were repeated bouts of bright bloody and tarry stools. During the next few years the patient had seven admissions to other hospitals and received in all about twenty blood transfusions. Periodically she developed edema of the face and ankles.

Six months prior to admission the patient began to suffer fractures of multiple ribs, a clavicle, an ulna and a radius, associated with minor traumata. The frequent use of Demerol for the intense pain resulted in the patient's addiction to the drug. Relatively normal and regular menstrual periods continued until nine months after the gastric resection at which time there was an abrupt cessation. Her weight had fallen from 140 to 65 pounds during the six years since gastrectomy.

FIG. 1. Photograph taken twenty-four hours after operation. Despite vigorous preparation for laparotomy and marked general improvement the emaciation is still apparent. The spontaneous ecchymoses in the skin of the forearms are visible.

Physical Examination: The patient was extremely emaciated. She suffered constant pain in many skeletal sites. There was a firm but crepitating round mass, measuring about 3 cm. in diameter, occupying the region of the proximal third of the left clavicle. This swelling was markedly tender. There were similar but smaller masses at the junction of the middle and distal thirds of the right radius and in the mid-axillary portion of the eighth rib on the right. All of these masses appeared to be part of the underlying bone. There was a moderate dorsal kyphosis.

There was pallor of the skin, nailbeds, and mucous membranes. The skin was loose and paper-like, and there were purplish, ecchymotic plaques in the superficial layers of the skin of the forearms (Figure 1), back, and abdomen.

The chest was slightly emphysematous, and the lungs were clear. Blood pressure was

105/62 mm. mercury. The only abnormalities in the examination of the cardiovascular system were a soft apical systolic murmur and atheromatous changes in the retinal arterioles. The abdomen was protuberant, and the abdominal wall very thin. There were no palpable masses or organs. Pelvic and rectal examinations were negative. Neurological examination failed to show any evidence of degenerative changes.

Laboratory Data: Serological tests for syphilis were negative. The urine was slightly cloudy, amber, and had a specific gravity of 1.012. No reducing substance was present, but there were sometimes traces of protein in the urine. Microscopic examination showed about 15 leucocytes per high-power field but no erythrocytes or casts. Tests with Sulkawitch reagent for excess urinary calcium were negative, as were tests for Bence-Jones protein. Urine cultures revealed a moderate growth of B. Coli-aerogenes.

The erythrocyte count was 3.0 million per cmm., hemoglobin 8.6 grams per cent, and hematocrit 27 per cent. The red cell indices were normocytic and normochromic. The appearance of the red cells on stained smear confirmed the findings of the indices. Leucocytes were 4400 per cmm. with a normal differential count. Bleeding, clotting, and prothrombin times were normal. Platelets were slightly reduced to 152,000 per cmm., and clot retraction was normal. The Rumpel-Leede tourniquet test was negative.

The non-protein nitrogen was 30 mg. per cent, fasting blood sugar 76 mg. per cent, CO_2 combining power 29.2 meq. per liter, and chlorides 94.2 meq. per liter. Sodium and potassium were 138 and 3.0 meq. per liter respectively. Cephalin flocculation, serum bilirubin, and thymol turbidity tests were all normal. Total serum protein was 4.1 grams per cent with an albumin of 2.4 grams per cent. Serum calcium was 8.1 mg. per cent, phosphorus 1.8 mg. per cent, and alkaline phosphatase activity 29.4 Bodansky units.

Plasma vitamin C level was 0.2 mg. per cent (normal range 0.7 to 1.2 mg. per cent). Vitamin C determination on the buffy coat layer was not carried out. Serum iron level was normal. There were, therefore, a hypoproteinemia, elevated alkaline phosphatase, and low calcium, phosphorus, and vitamin C concentrations.

The stools were bulky, pale, and mushy, containing many undigested meat fibers and starch and fat particles. Twenty-four hour stool collection obtained after the patient had been on a low fat diet, showed 30.2 per cent ether extractable solids.

X-ray films of the trunk and peripheral skeletal system showed a severe rarefaction of of all bones with multiple fractures and infractions. There was a coarsening of the trabecular pattern, but no significant periosteal reaction. Enormous callus formation was present at the site of the clavicular fracture, but there was only minimal calcium deposition at all fracture sites. Biopsy material from the left clavicular region revealed callus formation most of which showed osteoid without deposition of inorganic material. Smears of the sternal marrow were normal except for the presence of a few very large multinucleated giant cells. Histological section of the marrow was interpreted as showing hypoplasia of all elements.

Course in Hospital: The patient was in almost constant discomfort from the fractures, and it was necessary to continue Demerol injections frequently. On a low fat diet stools were reduced in frequency from about four to two daily and became more formed. However, sixteen days of this diet failed to elevate the serum phosphorus. When 100,000 units of oral calciferol daily were added to the diet, the serum phosphorus rose from 1.7 to 3.5 mg. per cent in four days.

It was felt that the patient was suffering from a severe degree of malnutrition and osteomalacia (adult rickets), both of which were direct results of chronic diarrhea. In view of the character of the stools immediately postoperative, and the time relationship between the onset of diarrhea and the gastric operation, the possible existence of a gastro-ileostomy was entertained.

Barium enema appeared entirely normal. Two upper gastro-intestinal x-ray studies were inconclusive. The findings of the first examination were confused by the presence of what was thought to be residual contrast medium from the recent barium enema. During the second study barium remained in the stomach for a period of many hours and prolonged fluoroscopy was impractical.

Dr. John F. Roach of the Department of Radiology suggested that barium be introduced into the small bowel through a Miller-Abbott tube. Figure 2 shows the final position of the

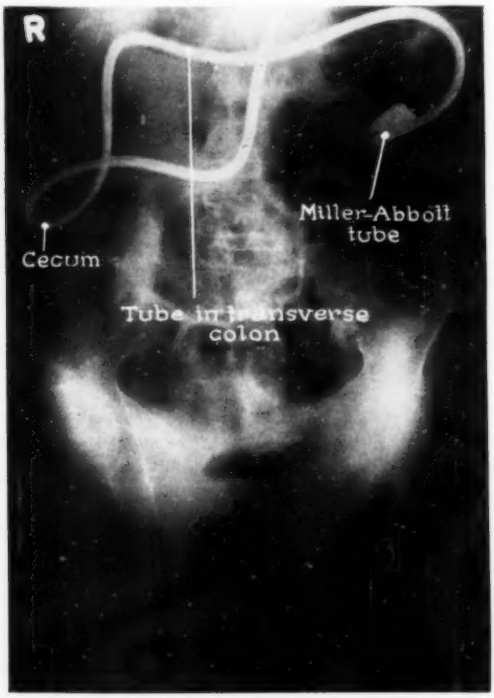

FIG. 2. Abdominal film showing the mercury bag of the Miller-Abbott tube lying in the splenic flexure of the colon. The tube can be traced directly to the caecum and follows the course of the colon.

tube *in situ*. The tube passed from the remaining gastric pouch directly to the right lower quadrant and then back in the course of the colon to the left upper quadrant. Here despite all efforts it was impossible to pass the tube farther. Barium was injected into the tube in this position and outlined a mucosal pattern typical of colon. The tube was withdrawn slowly under fluoroscopic visualization and barium continuously injected. At a point in the right lower quadrant corresponding to the position of the ileocaecal valve, increased resistance was encountered, but was overcome by a strong tug on the oral end of the tube. There was a similar delay at the site of the anastomosis. Figure 3 demonstrates the course outlined by the barium. Diagnosis of gastro-ileostomy appeared certain, and the segment of terminal ileum from stoma to caecum was estimated to be sixteen inches long.

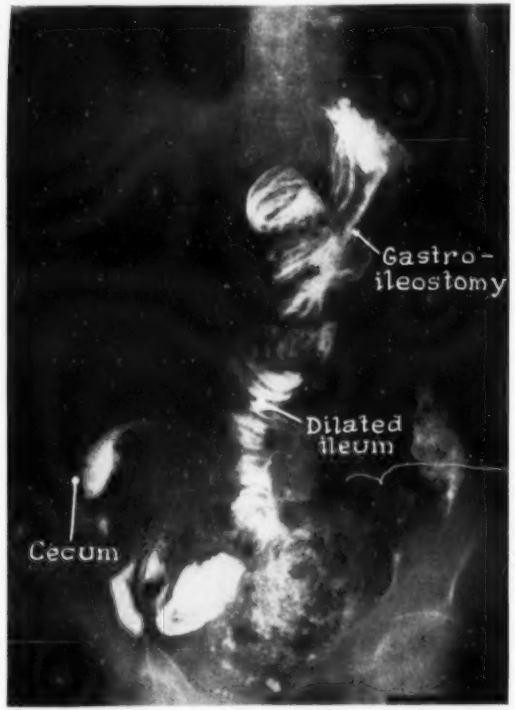

FIG. 3

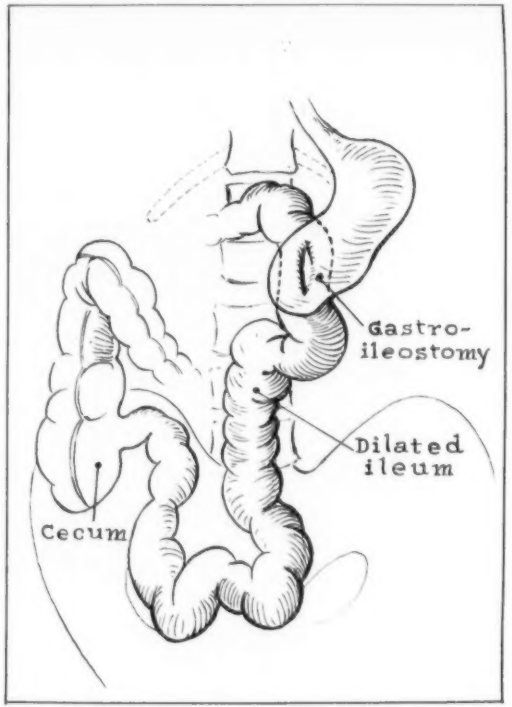

FIG. 4

FIG. 3. Barium injected during withdrawal of the intestinal tube has outlined and identified the caecum, dilated ileal segment, and gastro-ileostomy. Some barium is already present in the pelvic colon.

FIG. 4. Diagrammatic representation of the roentgenological findings shown in Figure 3.

The choice of therapy lay between a two-stage procedure with preliminary feeding through a jejunostomy and a one-stage corrective maneuver to be preceded by vigorous oral and intravenous replacement to make the operative risk reasonable. The latter course was selected. Oral feedings, consisting of protein hydrolysate, glucose and essential vitamins and minerals, were not tolerated because of severe abdominal cramps and increase in diarrhea. A limited low fat diet supplemented with intravenous feedings of glucose, amigen, minerals and vitamins soon led to a marked reduction in appetite and the appearance of edema. The weight gain from an initial 65 pounds to 75 pounds during this period was obviously associated with the onset of visible edema. The concentration of serum proteins failed to rise appreciably at this time. Whole blood transfusions corrected the anemia, but administration of both plasma and whole blood resulted in increased edema. Eventually however, this combined therapy did raise the total serum protein concentration from 4.1 to 5.3 grams per cent.

The opinion of the surgical staff was that risk of operation would be lessened by a more normal serum protein concentration. Intravenous human salt-poor albumin was therefore used and produced an immediate rise in the serum albumin fraction and in the total proteins. Twenty-five grams of human albumin were given on seven of ten days preceding operation with a rise in total protein level from 5.3 to 6.7 grams per cent. This corresponded approximately to a rise of 0.2 grams per cent protein per 25 grams of human serum albumin administered. Four days after this therapy was started the patient had lost 5 pounds and became free of visible edema. Although it was obvious that she was not in ideal condition for any operative procedure, nevertheless, it was thought that there was little to be gained in further delay. It was felt that a one-stage corrective procedure would be more satisfactory and result in a shorter period of convalescence than a two-stage maneuver employing a preliminary jejunostomy.

Operation: Laparotomy, using nitrous oxide and ether as anesthesia, was performed on February 21, 1950, eleven weeks after admission. The peritoneal cavity was free of adhesions. The gastric pouch was readily identified and the anastomosis proved to be of an antecolic Polya type. There was no evidence of stomal ulcer. The dilated distal segment was traced toward the caecum and proved to be no more than eighteen inches in length. The excluded segment of ileum and jejunum was grossly normal. There was no congenital anomaly in the attachments or position of the viscera.

The anastomosis was resected between clamps removing a cuff of stomach and a wedge of ileum. An end-to-end anastomosis of the ileum was performed following which a retrocolic Hofmeister gastro-jejunostomy was completed and a biopsy of the liver taken. The liver appeared grossly and microscopically normal. Of some concern during operation was the rapid appearance of edema in the mesentery and on the serosal surface of the bowel. At the completion of the procedure the mesentery was about two centimeters thick and was waterlogged despite minimal manipulation. A constant infusion of concentrated human serum albumin was administered during the operation.

Postoperative Course: The patient did well after operation. On the second day feedings of skimmed milk, 30 cubic centimeters hourly, were started through a nasal tube which had been threaded into the jejunum at operation. This amount was gradually increased, and on the ninth day the patient was started on a soft diet. Thereafter there was a progressive gain in weight. By the third week she was able to tolerate a regular diet. Twenty-five days after the operation she passed a normal stool, and bowel function has continued normally.

Gastro-intestinal series on the twenty-eighth postoperative day showed a normally functioning gastro-jejunostomy. The large doses of vitamin D were reduced to 1000 units daily after operative correction for fear of vitamin D intoxication. The patient developed

no more fractures, and her addiction to Demerol was gradually overcome. No visible edema was noted during the postoperative period. Serial roentgenograms since operation have revealed slow progressive increase in density of the bones, marked improvement in the trabecular pattern, and healing of all the fractures. The cutaneous ecchymoses of the forearms and back regressed slowly. When the patient was discharged, she weighed 104 pounds

FIG. 5. Photograph taken six months after operation and after the patient had gained 53 pounds. She was able to stand without support for the first time in over a year. Ecchymotic lesions on the forearms have disappeared.

—a gain of 34 pounds in the 76 days after operation. She was ambulatory and in exceedingly good spirits.

Figure 5 shows the patient three months after discharge. She remains in good health, doing the housework and cooking for her family. Her weight was 121 pounds and the hematocrit 41. At first weight gain was more pronounced on the trunk, but later involved the extremities as well. Seven months after operation the patient experienced her first menstrual period in six years. Menstruation has continued normally and regularly.

The serum calcium rose to 10–11 mg. per cent after operation. Serum proteins were 6.7 grams per cent on discharge with an albumin of 4.3. Serum phosphorus levels were 4.0 to

5.1 mg. per cent. Alkaline phosphatase remained elevated at approximately 15 Bodansky units. Vitamin C levels were not determined after operation.

COMMENT

Gastro-ileostomy in association with gastric resection results in profound gastro-intestinal dysfunction. By contrast inadvertent gastro-ileostomy without resection need not result in this degree of disability because direct passage of food through the duodenum and jejunum is not necessarily permanently precluded (2). Indeed, some patients have survived several decades or more after simple gastro-ileostomy with very little disability. Our patient's history is unusual in that the short-circuiting anastomosis existed for six years uncorrected after gastric resection. The longest previously recorded survival was that of Moretz's patient (2) whose corrective surgery was performed eighteen months after the gastric resection and gastro-ileostomy. However, it is quite possible that our patient's long survival resulted from reflux of some food into the excluded loop of small intestine and some absorption of nutrients through this segment of gut. This possibility is suggested by the reflux of barium into this excluded loop during x-ray studies and by the fact that this portion of gut functioned normally after corrective surgery.

The delay in establishing the correct diagnosis in our patient reflects the limitations of ordinary roentgenographic techniques. The method which was finally used should be applicable in the study of any patient suspected of having gastro-enteric fistula. A Miller-Abbott tube was passed through the gastric pouch and into the small intestine where peristalsis carried the tube into the colon. A thin suspension of barium injected into the tube as it was withdrawn identified and defined the ileal segment. Previous fluoroscopic attempts had failed either because barium lingered for many hours in the gastric pouch or because there may have been reflux into the excluded loop of ileum, jejunum and duodenum. Brown, Colvert, and Brush (3) have already commented on these roentgenological findings in patients with gastro-ileostomy.

The method of preparation of this patient for operation deserves brief comment. A two-stage procedure with preliminary feeding jejunostomy was not used, because it was felt that this maneuver carried as great a risk as a one-stage corrective operation and probably would result in a longer period of convalescence. Anemia was corrected by whole blood transfusions. Transfusions were, however, unsatisfactory in overcoming the protein deficiency as increased edema appeared after many of the transfusions. Salt-poor human albumin provided protein in the best form available under the circumstances. Total serum protein concentration and albumin-globulin ratio were restored to normal and visible edema disappeared in less than ten days with seven intravenous infusions of 25 grams of albumin.

The corrective operation was accomplished in one stage without preliminary

jejunostomy. Whereas the patient reported by Moretz (2) had a congenital malrotation of the intestine, no such anomaly was noted in our patient to account for the original mistake. The source of the repeated gastro-intestinal hemorrhages which occurred early in her illness was not found at laparotomy. Ecchymotic skin lesions have long been described in all forms of chronic inanition. The possibility that the gastro-intestinal hemorrhages were associated with the generalized capillary fragility seen in chronic inanition must be considered. It is of interest, however, that although vitamin D deficiency was clearly present in our patient, vitamin K, another fat-soluble vitamin, had apparently been absorbed in sufficient quantities as evidenced by the normal prothrombin time. This is in contrast to the hypovitaminosis of all fat-soluble vitamins following multiple resections of small bowel for an inflammatory lesion in the patient reported by Albright and Stewart (4).

The multiple fractures were the chief cause of the patient's discomfort. Diarrhea may result in disturbance of calcium and phosphorus metabolism with either a normal or low serum calcium concentration (5). According to the nomogram of McLean and Hastings (6), the diffusible fraction (i.e. that which actually bathed the cells) of our patient's serum calcium might be considered essentially normal since the protein concentration was reduced to 4.1 grams per cent. The chemical pattern in our patient was therefore one of normal calcium, low phosphorus, and increased alkaline phosphatase concentration, the type commonly seen in juvenile rickets and adult osteomalacia. The biopsy obtained from the mass in the area of the fractured clavicle disclosed osteoid tissue (uncalcified callus) with very little calcification in it. Serum phosphorus concentration remained low during the two weeks that the patient was given a low fat diet, despite the fact that the number of stools was reduced by this regimen. However, the oral administration of 100,000 international units of calciferol was followed promptly by a rise in serum phosphorus from 1.7 to 3.5 mg. per cent.

It seems clear that the patient's skeletal difficulty was osteomalacia due to low serum phosphorus, and that this low phosphorus was dependent upon an insufficiency of vitamin D and not due to the diarrhea *per se*. After operation the progression of fractures and continuance of bone pain were halted. Serial roentgenograms have revealed progressive improvement in the trabecular pattern and density of the bones.

SUMMARY

An unusual case of gastro-ileostomy inadvertently performed at the time of gastric resection is described. The patient survived for six years before the surgical error was discovered and corrected. During this time she suffered from severe diarrhea with resultant advanced malnutrition and osteomalacia. Passage of an indwelling intestinal tube through the anastomosis and injection

of barium through the tube during withdrawal provided conclusive evidence of a gastro-ileostomy. A one-stage corrective procedure was performed rather than a two-stage maneuver with preliminary jejunostomy. Recovery following the operation was dramatic. The excluded segment of small intestine functioned normally, when, after six years, it was connected properly to the gastric pouch.

Addendum: Diagnostic studies and procedures to prepare the patient for corrective surgery were carried out under the guidance of Dr. John E. Howard of the Department of Medicine. The authors also wish to express their appreciation to Dr. Howard for invaluable aid in the preparation of the manuscript.

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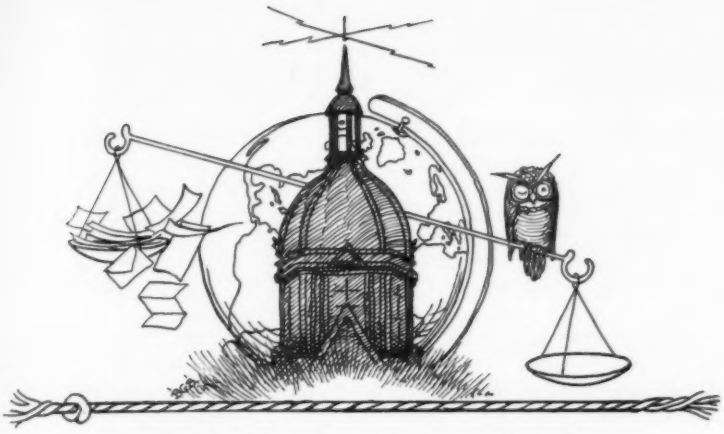

BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of the Bulletin)

The Kidney. Structure and Function in Health and Disease. By HOMER W. SMITH. 1049 pp. $12.50. *Oxford University Press, New York.*

This book cannot be considered in any way as a revision of the author's well known 1937 book on "The Physiology of the Kidney." Although necessarily based on his previous treatise, it is much more extensive as the title indicates. A large part of the preface is taken word for word from the introductory chapter of the 1937 book. The excellent brief historical account of the theories of renal function, which is here given as a prologue, is a reproduction of the third chapter of the previous book. However, it is so well done, that one would not want to see it changed. The reviewer must quote what he considers to be the most pregnant sentence of this prologue. It is as follows: "But in the interim, Cushny's modern theory had accomplished the main thing the author had desired for it: it had served to guide investigators so that they could ask intelligent questions about the kidney and hope for intelligible answers; which is, of course, the chief function of any theory."

The nine hundred pages of text are divided into four parts. The first is concerned with the basic physiology of the kidney; namely, anatomy of the mammalian kidney, evidence for the accepted filtration-reabsorption-secretion theory of urine formation, clearances and their use in measuring quantitatively filtration, reabsorption, secretion and renal blood flow, and a catalogue of information on the clearances of various substances. A discussion of the reliability of the inulin clearance as a measure of glomerular filtration is left until the end of this section. In part two, the excretion of strong electrolytes, and acid-base equilibria in relation to the excretion of acid as well as the influence of the neurohypophysis and adrenal cortex on the excretion of urine are discussed. Part three contains a mixture of somewhat unrelated topics. These are: the control of the renal circulation; the influence of endocrines, vitamins, and diet on renal function; renal function in infancy and its maturation; the comparative physiology of the kidney from the lowly fishes to man; and a chapter, prepared with the assistance of Dr. Gomez, on some problems of renal hemodynamics.

Part four is concerned entirely with studies of renal function in abnormal conditions and in disease.

The bibliography contains 2300 references. It is interesting that, with the exception of about a dozen, all refer to papers published in the past three decades. Although references to earlier papers can be found in Cushny's "The Secretion of the Urine," it is regrettable to the reviewer that the flood of modern literature has precluded reference to many earlier papers. A student could still read with great profit the classical papers of Bowman, Starling and others.

In presenting the evidence for filtration and reabsorption, the author gives only the direct evidence obtained from studies on individual nephrons, and omits the large amount of circumstantial evidence which had accumulated before these studies were made (this is discussed in his former book). When the specific problem of measuring the filtration rate is taken up, one is introduced almost immediately to inulin as the final answer of the problem. Some may regret that the chronological approach was not used in both these matters: there might be some discussion of the older investigations of such masters as Starling and Cushny and a discussion of the development of the measuring of the filtration rate from the important investigations of Mayrs and Rehberg in the early nineteen-twenties. However, the earlier investigations of filtration rate are discussed in later sections. The reviewer is inclined to accept the method of presentation, which has been used, as more satisfactory than the chronological one for the beginning student of renal physiology. The anatomy of the amphibian kidney in as far as it differs from that of the mammalian might have been discussed before the investigations on individual nephrons of the frog and mud-puppy are presented.

In the discussion of the validity of the inulin clearance as a measure of glomerular filtration rate, the author states, "In summary, no single line of evidence cited above is absolute—indeed it is impossible to obtain absolute proof of any hypothesis. But the total evidence can be best explained by the interpretation that the inulin clearance in all species is identical with the filtration rate." It is unfortunate that the difficulty in interpreting the clearances of inulin and creatinine in man is not given in this chapter. In a previous chapter, in discussing the clearance of creatinine we find: "However, the excretion of creatinine in man is complicated by a factor not as yet reported in its excretion in other species or in the tubular excretion of other substances in man: namely, in other species the creatinine/inulin clearance ratio, after being depressed by elevation of the plasma creatinine level, rises again to its initial value as fast as the plasma level is reduced by excretion; this is the result to be expected in terms of a reversible tubular transfer mechanism limited by a maximal rate, the reduction in the clearance ratio being simply an expression of the relative values of the numerator and denominator in the fraction $P_{cr}C_f/Tm_{cr}$. In man, however, the creatinine/inulin clearance ratio fails to rise as the plasma creatinine concentration is reduced by excretion, but remains for a number of hours at a value of 1.1 to 1.2." This is an indication that the field is not closed, but more investigation along new lines is needed.

The chapter on the antidiuretic hormone of the neurohypophysis presents clearly the facts that have accumulated concerning this important regulator of water excretion and it is quite clear that the author appreciates the uncertainties in regard to interpretations. In fact, very early in the chapter he writes: "The subject got off to a bad start and has been marked by many contradictory results and theories—Fisher, Ingram, and Ranson remark that the history of diabetes insipidus reads like a comedy of experimental errors, and the recent report of Bykow that neither conditioned water diuresis nor conditioned inhibition of diuresis is abolished unless both hypophysectomy and renal denervation are carried

out reveals that the problem is not yet free of the possibility of error." The site of action of the antidiuretic hormone is assumed to be the distal tubule. This leaves unexplained why, although this hormone occurs in the pituitaries of all classes of vertebrates, it is only in birds and mammals that it increases the tubular reabsorption of water. The distal tubule occurs in all classes of vertebrates, although it may be lacking in some species of fishes, while the loop of Henle occurs only in birds and mammals.

The chapter on the comparative physiology of the kidney is particularly valuable in that it not only describes renal function in various classes of vertebrates—fishes, amphibia, reptiles, birds, and mammals—but ends with a most interesting comparison of the mammals—desert mammals, aquatic mammals, and the ordinary and the exotic laboratory mammals. A quantitative approach to renal function in mammals is given as far as present data permit.

The last part of this book on renal function in abnormal conditions and in disease is introduced by an excellent chapter on the limitations of clearance methods during disturbed renal function. After reading this entire section of the book, one wonders if some of the workers in this field of abnormal function have taken cognizance of these and previous warnings as to interpretation of data obtained by clearance methods in diseased states. In this last section, the author stays well within what one would expect from the title of the book. Pathology is mentioned only enough to give a background. The data are clearly and fairly presented in an objective way without speculation and the reader sees that usually the final answer cannot be given on account of lack of knowledge. An attempt is then made to evaluate critically just what conclusion, if any, can be drawn from the frequently conflicting data. These discussions by a physiologist, of renal ischemia, crush syndrome, shock, "lower nephron nephrosis," and congestive heart failure might serve to clarify the ideas of many clinicians in regard to these abnormalities.

The whole subject of the kidney is so well handled that one is a little hesitant to introduce further critical notes. However, the reviewer wonders if sufficient space is given to a discussion of the facts which either do not agree with current theory or seem to offer a point of departure for the advances of the next decade or two. The three-way passage of substances—filtration, reabsorption, and secretion—which seems to be true in regard to potassium and thiosulfate is contrary to the assumption of the current theory that there is only a one-way passage across the tubule. In view of this, one wonders if the proximal tubule may not secrete water under normal conditions in the mammalian kidney (in view of the aglomerular tubule of fish, Chamber's work on tissue culture, and Oliver's finding of aglomerular tubules in the pathological kidney). The so-called "denervation diuresis" which has been obtained only in anesthetized animals is dismissed by saying that it "appears to be a release from enhanced vasoconstrictor tone engendered by anesthesia and traumatic operative procedure." However, if one accepts the validity of clearances to measure glomerular filtration rate and renal blood flow, one finds that the denervated kidney under anesthesia shows an increase neither in filtration rate nor in renal blood flow despite an excess excretion of water and certain urinary bodies. This, of course, is opposed to blood flow measurements by mechanical methods. It is also interesting to recall that no function has been assigned to the nerve endings which have been found on and between the tubule cells. In addition, the work of Mudge and Taggart showing that infusion of acetate or lactate can markedly increase Tm_{PAH} makes one wonder how accurately the Tm is a measure of effective renal excretory tissue.

There are extremely few errors, typographical or otherwise. On page xvi (in the prologue) the date of Bowman's classical paper is given as 1832 (instead of 1842). On page 256, we find antropinization instead of atropinization. In reference 625, the data of publication

is omitted. On page 244, dog is given instead of cat and a specific gravity of 0.050 instead of 1.050. On page 25, phosphate is stated to be reabsorbed by the distal instead of the proximal tubule.

This book is a compendium of available knowledge of the kidney. It contains a wealth of information which has been more or less woven into a definitive quantitative theory of renal function. To students and research workers in the field of renal physiology, it is a "MUST."

E. K. MARSHALL, JR.

An Introduction to Universal Serologic Reaction in Health and Disease. By REUBEN L. KAHN. 158 pp. $3.50. *The Commonwealth Fund, New York.*

In the present volume, Dr. Kahn develops the thesis that tissue lipids, liberated during the course of cellular metabolism stimulate the production of auto-antibodies. These antibodies are detectable in all sera, in health and disease, thus providing the basis for the term, "Universal Serologic Reaction." The standard Kahn antigen, a crude alcoholic extract of beef heart tissue, is used for the estimation of the auto-antibodies at two different temperatures in the presence of varying concentrations of sodium chloride. The results of the test are expressed graphically in the form of flocculation patterns which are considered distinctive for the normal individual. Significant alterations in the patterns are also recorded for syphilis, yaws, leprosy, tuberculosis and malaria. These pattern variations, presumably unique for each disease entity, are thought to be mediated by specific lipid antigens all of which are present in the beef heart extract.

This concept of antibody production to host tissues has gained familiarity in efforts to explain the origin of the Wassermann antibody. The author's extension of this hypothesis to other diseases is based largely on empirical findings and is supported in part by data correlating the degrees of precipitation with the severity of the disease process, notably in tuberculosis and in experimentally induced malaria. This relationship has not as yet been established for syphilis.

The evidence pertaining to the specificity of the universal reaction is somewhat less conclusive. Although successive tests performed at different intervals, indicate progressive and apparently significant pattern variations for any one disease, the patterns emerging from a single test lack differential diagnostic import. This limitation is recognized by the author and is clearly evident from the overlapping patterns observed both in health and disease.

Since an antigen-antibody mechanism has been invoked for the universal reaction, a more direct immunochemical approach to the problem of disease-specific antigenic lipids should be considered. Studies directed towards the isolation and characterization of the individual lipid antigens could provide the necessary data for a critical evaluation of the working hypothesis outlined in this book. Experiments designed to demonstrate the presence of the several antigens in beef heart extracts by means of antibody absorption tests might also be rewarding as would detection of the specific auto-antibodies by technics other than the flocculation reaction. In the absence of pertinent data of this type, one can merely agree with the author in saying, "Only by trial can the applicability of the universal reaction in disease and health be ascertained."

A. G. O.

Methods of Vitamin Assay, 2nd edition. Prepared and edited by The Association of Vitamin Chemists, Inc. 301 pp. $5.50. *Interscience Publishers, New York.*

The second edition of "Methods of Vitamin Assay" has been expanded to include pantothenic acid, pyridoxine, folic acid, vitamin B_{12} and niacin, in addition to those published in

the first edition. The inclusion of these methods will no doubt increase the usefulness of the book, as judged by the wide acceptance of the first edition.

This book which is intended merely as a manual for the analyst is edited by a group of competent specialists. At the beginning of each chapter one finds condensed information about the chemical properties of a given vitamin and the discussion of other available methods. The prudent selection of only the widely accepted and used methods will be extremely valuable to the investigators who are interested primarily in using the assay as a tool.

The brief description of the principle involved in and the equipment necessary for a given vitamin should be helpful to the assayists in making intelligent execution of the procedures which are described with clarity and in detail. This book should be most useful in the laboratories where bioassays are routinely carried out.

B. F. C.

A Year with Osler. By JOSEPH H. PRATT. 209 pp. $4.00. *The Johns Hopkins Press, Baltimore, Md.*

Great teachers of medicine are rare indeed and Dr. Pratt has performed a great service in giving us so clear a picture of one of the greatest of them all, William Osler. As a student at Hopkins when the "Chief" was at the height of his physical and mental vigor he managed to keep of that year not only the admiring and affectionate memory of the Professor of Medicine which remains with all of Osler's students, but a unique and most interesting day-by-day record of the method and as well the substance of Osler's teaching. To read these notes brings to the mind of any former student of the master clear and vivid pictures of the man himself and of the clinics and demonstrations in which he was the central figure. They give also most interesting evidence of the differences in both the matter and the manner of the medical teaching of the last years of the 19th century as compared with that of today. The predominance of typhoid fever, malaria, pneumonia and syphilis among the cases selected for presentation in the clinic reflects the overwhelming importance of these diseases half a century ago and reflects also the lack of recognition of so many of the conditions with which the present day clinician must concern himself.

As to the method of Osler's teaching, Dr. Pratt makes obvious to his readers the great importance Osler attached to the taking of an accurate and complete history of the patient and his disease and to the making of a careful and detailed inspection of the individual as a whole before beginning a detailed examination of the separate organs and regions. Laboratory examinations played, at the time these notes were made, a relatively small part in diagnosis and Osler's principal effort seems to have been to integrate all the significant observations into the picture of a single disease process.

Any physician who is engaged in teaching clinical medicine to students whether undergraduate or graduate will find much that is helpful in this interesting volume.

A. W. F.

The Mask of Sanity, 2nd edition. By HERVEY CLECKLEY. 569 pp. $6.50. *The C. V. Mosby Co. St. Louis, Missouri.*

In this second edition, Dr. Cleckley presents "an attempt to clarify some issues about the so-called psychopathic personality." It is divided into five sections and three appendices, in an effort to pursue a scientific approach to a psychiatric disorder notorious for its vagueness in all ways, but particularly for its resistance to psychotherapy. Section 1, "An Outline of the Problem," simply and honestly declares the difficulties involved, points to the psychopath as genuinely ill, and urges correction of the negative attitudes toward psycho-

paths commonly aroused in others. Section 2, "The Material" presents many cases in selective detail. Two noteworthy omissions in the case histories are family interrelationships and description of the early childhood. Section 3, "Cataloging the Material," compares the psychopath with other emotionally sick people and lists sixteen characteristic signs of the disorder. Section 4, "An Attempt at Interpretations," gives the author's views on etiology and pathology. Mainly, psychopathic personality is labeled a "semantic disorder," and its psychopathology is considered to be not obvious. Section 5, "What Can Be Done?," makes some suggestions, (e.g.—revising medicolegal considerations), and stresses the need for more far reaching efforts to deal with the problem.

Some general comments may be made. Although lengthy and somewhat laborious to read, the book is interestingly written. It is richly documented with case histories and bibliography (226 in number). It shows clearly the magnitude of the problem presented by the psychopath. The attempt to be detailed and scientific seems, however, to ricochet with wordiness and lack of clarity. It may not be too useful to those outside the psychiatric field.

L. J. G.

Medical Neuropathology. By I. MARK SCHEINKER. 372 pp. $10.00. *Charles C. Thomas, Springfield, Illinois.*

This is the third of a series of three monographs written by the author on neuropathology. The first entitled "Neuropathology" appeared in 1947, the second "Neurosurgical Pathology" was published a year later. In this volume, it is the purpose of the author to bridge the widening gap between neuropathology and general pathology by correlating the cerebral and general systemic manifestations of the more common diseases of internal medicine. Accordingly the first three chapters of the monograph are devoted to the cerebral complications of cardiovascular disease. A separate chapter is devoted to the changes in arterial hypertension. The encephalopathies caused by chemotherapy and exogenous toxic agents are presented. The neuritides are described with reference to the more common disease entities. The pathological changes found in the central nervous system in the various blood dyscrasias are the subject of one chapter. There is intentional emphasis upon the vascular disorders, especially those which the author considers functional or reversible. The concepts of vasoparesis and vasoparalysis are elaborated much as the author has done in his previous writings. The entities would be more realistic if their relationship to pathophysiological states such as sludging was demonstrated.

The monograph presents the author's personal opinions based on a large experience in a general hospital. Although references are made to the German and American literature the author makes little attempt to discuss controversial issues, which would add interest for the general pathologist and spice for the neuropathologist. However, on most subjects the author's viewpoint coincides fairly well with currently accepted neuropathology. In spite of the fact that the author appreciates the biological characteristics of cerebral pathology, as may be inferred from his discussion of functional vascular disturbances, his presentation of the material lacks the dynamic approach which follows the disease process from insignificant changes to frank pathology describing the alterations which are operative in the lesion itself and those which are secondary to the lesion.

The monograph is well illustrated by 186 figures, all but one in black and white. A short bibliography is appended. The general format of the book is pleasing.

The monograph, presenting the neurological manifestations of systemic disease, should be of value to students and postgraduate workers in pathology and neurology. With the author's two previous works on general and surgical neuropathology it forms atriad of valuable monographs which every neuropathologist should have available for reference.

A. E. W.

Proctology in General Practice. By J. PEERMAN NESSELROD. 276 pp. $6.00. *W. B. Saunders Co., Philadelphia, Pa.*

This excellent volume does more than its title implies, for it provides a splendid text on Proctology for the surgeon as well. In line with the increasingly recognized importance of proctoscopic examination as a part of a thorough diagnostic survey, the author presents a well conceived chapter on Diagnostic Procedures wherein the details of endoscopic examination and related matters are put forth in a most readable and acceptable form. Any diagnostician, be he medical or surgical, who is active or proposes to be active in this field would profit from a study of this section. In a later chapter on Clinical Proctoscopy, detailed descriptions of the various pathologic states are presented. Illustrations in both black and white and in color are included as a further visual aid; the colored pictures doubtless being derived from the admirable colored moving pictures by Garner and Nesselrod which have been widely shown. The author emphasizes repeatedly his concept of anal infection, originating in the obscure anal ducts, as the prime etiologic factor not only in the inflammatory conditions, but in hemorrhoidal disease as well. Detailed surgical procedures are elaborated with the several pathological entities as they are described. The meticulous post-operative care, practiced by the author, illustrates his attention to detail, yet will be criticized by some as being unnecessary. The subject matter is of readable length (276 pages), nicely illustrated and presented, and represents a happy balance between the personal practices and experiences of the author and the recorded experiences of other authorities to whom generous reference is given.

S. McL.

Surgery of the Shoulder. By ANTHONY F. DEPALMA. 438 pp. $17.50. *J. B. Lippincott Co., Philadelphia, Pa.*

This volume is an excellently illustrated comprehensive source book on the shoulder. It is replete with excellent photographs and original drawings, conveniently placed to the printed material they are intended to clarify and demonstrate. The x-ray reproductions are unusually clear.

The concept of limiting a book to a single region such as the shoulder is a very practical one. It simplifies reference work.

This volume has an extensive bibliography after each chapter. It amplifies with due mention the established work of Codman and others. The work on variational anatomy and lesions of the shoulder joint and tendon cuff at various ages is a great, original contribution. The method of obtaining this material and the painstaking preparation of the many specimens is a monumental piece of practical research and observation.

The material on "Frozen Shoulders," may lack the complete agreement of investigators in this problem but it offers a very plausible explanation and an even more practical management of the patient. The common and uncommon lesions of the shoulder region are presented and discussed proportionately. Treatment throughout demonstrates the author's wide experience with clinical problems and complications due to treatment itself.

The discussion on the etiology of recurrent or habitual dislocation of the shoulder is based on sound observation and the advocation of an operation limiting external rotation, is a logical sequel to these observations. His condemnation of the Nicola operation and associated criticism of common residual discomfort is not universally shared.

The differential diagnosis of referred shoulder pain is again a most practical reference section. Surgical approaches and procedures are illuminatingly illustrated with excellent drawings, legends, and appropriate comments. The index is accurate and complete. "Surgery of the Shoulder" is an eminently useful and practical reference text.

E. J. McD.

A Textbook of the Practice of Medicine, 8th edition. By VARIOUS AUTHORS. Edited by Frederick W. Price. 2076 pp. $9.00. *Oxford University Press, New York.*

Since its first edition in 1922, Price's Practice of Medicine has been as distinguished in the United Kingdom as have been the texts of Osler and of Cecil in the United States. The eighth edition continues in the tradition of its predecessors, and therein lies its strength and, in a small way, its weakness.

In a sense, it is presumptuous for a reviewer to assess in detail the specialized contributions of physicians who have intimate knowledge of a group of diseases. There is no doubt that in this more compact volume at least as many medical facts have been assembled as are offered in our bulkier and more expensive textbooks. Nor has there been any sacrifice of readibility for conciseness; some sections, written from penetrating personal experience, have a pleasant flavor often lacking in the antiseptic jargon of many American communications.

Any single-volume textbook of medicine is uneven. In this one the sections on tropical diseases and on diseases of the skin are particularly thorough, and the section on diseases of the nervous system has no superior in any such text.

The philosophy of the volume is dedicated essentially to descriptive medicine, and within this framework it is particularly successful. The inquisitive student, however, will be dissatisfied with those portions that simply catalogue diagnosis, prognosis and treatment. Admittedly much of medicine remains descriptive. Yet many students of disease have posed the question why and, although their answers are not always correct, complete or changeless, sufficient physiological foundation has been constructed to permit reason to replace rote.

Finally, the volume provides opportunity to compare British and American medicine. The description of the sick is, of course, universally applicable. The approach to diagnosis appears to be similar. As might be anticipated, differences of opinion occur more commonly in treatment. In most instances where a "specific" agent is available there is agreement. An exception is noted in syphilotherapy. American writers do not hesitate to rely upon penicillin alone whereas Col. L. W. Harrison, the contributor to the British text, recommends combined arsenical and penicillin therapy. Technique of supportive therapy is often offered in elaborate detail, an enormous practical advantage, but some of the measures seem strange although the reviewer cannot judge their usefulness. Thus, in the symptomatic treatment of one of the acute infectious diseases a mustard plaster to the epigastrium is recommended for hiccough and champagne is suggested in event of vomiting. O, to be in England now that fever's here.

K. L. Z.

BOOKS RECEIVED FOR REVIEW

Angewandte Und Topographische Anatomie. By G. ZÜRICH. 416 pp., Ganzleinen DM 70.—$16.65). *Georg Thieme Verlag, Stuttgart, Germany.*

Annual Review of Medicine. Vol. II. Edited by W. C. CUTTING. Associate Editor, H. W. Newman. Editorial Committee, A. Blalock, J. S. L. Browne, A. M. Butler, E. M. MacKay and S. C. Madden. 485 pp. $6.00. *Annual Reviews, Inc., Stanford, California.*

Clinical Laboratory Methods, 4th edition. By W. E. BRAY. 614 pp., $7.25. *The C. V. Mosby Co., St. Louis, Missouri.*

Connective Tissues. Transactions of the First Conference, April 24–25, 1950. Edited by CHARLES RAGAN. 164 pp., $3.25. *Josiah Macy, Jr. Foundation, New York.*

Cybernetics. Transactions of the Seventh Conference, March 23–24, 1950. Edited by HEINZ VON FOERSTER. 251 pp., $3.50. *Josiah Macy, Jr. Foundation, New York.*

The Diagnosis and Treatment of Adrenal Insufficiency, 2nd edition. By GEORGE W. THORN. 182 pp., $5.50. *Charles C. Thomas, Springfield, Illinois.*

Diseases in Old Age. By ROBERT T. MONROE. 407 pp., $5.00. Harvard University Monographs in Medicine and Public Health, 11. *Harvard University Press, Cambridge, Massachusetts.*

Factors Regulating Blood Pressure. Transactions of the Fourth Conference, February 23–24, 1950. Edited by BENJAMIN W. ZWEIFACH AND EPHRAIM SHORR. 219 pp., $3.00. *Josiah Macy, Jr. Foundation, New York.*

Handbook of Nutrition. A Symposium. Prepared under the Auspices of the Council on Foods and Nutrition of the American Medical Association. 2nd edition. 717 pp., $4.50. *The Blakiston Co., Philadelphia, Pa.*

A History of Neurological Surgery. Edited by A. EARL WALKER. 583 pp., $12.00. *The Williams & Wilkins Co., Baltimore, Md.*

Nerve Impulse. Transactions of the First Conference, March 2–3, 1950. Edited by DAVID NACHMANSOHN. 159 pp., $3.00. *Josiah Macy, Jr. Foundation, New York.*

Pharmacognosy. The Study of Natural Drug Substances and Certain Allied Products. By ROBERTSON PRATT AND HEBER W. YOUNGKEN, JR. 644 pp., $8.50. *J. B. Lippincott Co., Philadelphia, Pa.*

Post-Graduate Lectures on Orthopedic Diagnosis and Indications. Vol. II. By ARTHUR STEINDLER. 208 pp., $6.00. *Charles C. Thomas, Springfield, Illinois.*

Problems of Aging. Transactions of the Twelfth Conference, February 6–7, 1950. Edited by NATHAN W. SHOCK. 215 pp., $3.50. *Josiah Macy, Jr. Foundation, New York.*

Problems of Consciousness. Transactions of the First Conference, March 20–21, 1950. Edited by HAROLD A. ABRAMSON. 200 pp., $3.00. *Josiah Macy, Jr. Foundation, New York.*

Problems of Infancy and Childhood. Transactions of the Fourth Conference, March 6–7, 1950. Edited by MILTON J. E. SENN. 181 pp., $2.50. *Josiah Macy, Jr. Foundation, New York.*

Roentgen Manifestations of Pancreatic Disease. By MAXWELL H. POPPEL. 389 pp., $10.50. *Charles C. Thomas, Springfield, Illinois.*

Selected Writings of Sir William Osler. 12 July 1849–29 December 1919. With an Introduction by G. L. Keynes. 278 pp., $4.00. *Oxford University Press, New York.*

A Textbook of Medicine, 8th edition. Edited by RUSSELL L. CECIL, ROBERT F. LOEB. Associate Editors: Alexander B. Gutman, Walsh McDermott, Harold G. Wolff. 1627 pp., $12.00. *W. B. Saunders Co., Philadelphia, Pa.*

Veterans Administration Technical Bulletins. Series 10. Vol. 4, 1950. 140 pp. *Veterans Bureau, Washington, D. C.*